

The American Journal of Cardiology

JUNE 1, 1990

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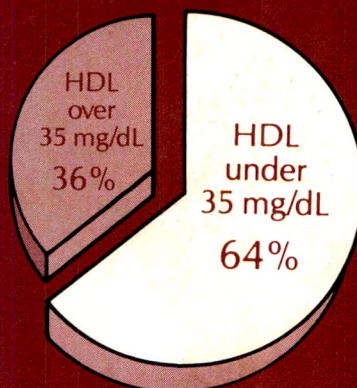
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The American Journal of Cardiology

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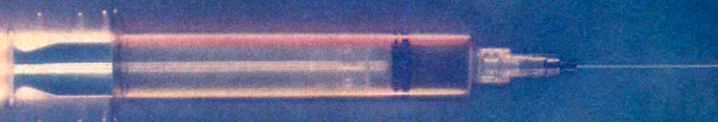
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CORONARY ARTERY DISEASE**1287****Propranolol-Induced Lipid Changes and Their Prognostic Significance After a Myocardial Infarction: The Beta-Blocker Heart Attack Trial Experience**

Robert P. Byington, Janine Worthy, Timothy Craven, and Curt D. Furberg

Data from the Beta-Blocker Heart Attack Trial were analyzed to determine the long-term lipid-altering effects of propranolol in patients after myocardial infarction. After adjusting for lipid level, change in lipid level and treatment group/lipid level interaction, the propranolol-induced reductions in mortality remain on the order of 20% during the period of the study. Thus, propranolol remains an effective prophylactic treatment for patients after MI despite a metabolic effect on serum triglycerides and high density lipoprotein cholesterol.

1292**Mechanism of Acute Myocardial Infarction in Patients with Prior Coronary Artery Bypass Grafting and Therapeutic Implications**

Cindy L. Grines, David C. Booth, Steven E. Nissen, John C. Gurley, Kim A. Bennett, William N. O'Connor, and Anthony N. DeMaria

Although acute myocardial infarction is usually due to thrombotic occlusion when involving a native coronary artery, the mechanism responsible for AMI in patients with previous coronary artery bypass grafting is not well understood. Since knowledge of pathophysiology of AMI may alter subsequent management, angiograms obtained between 1 hour and 7 days of AMI (median 1 day) were reviewed in 50 patients ≥ 1 year after coronary artery bypass grafting. Data indicate that in patients who have undergone previous coronary artery bypass grafting, AMI is usually caused by thrombotic occlusion of a saphenous vein graft and that conventional intravenous thrombolytic therapy may be inadequate to restore flow.

1297**Hemodynamic and Oxygen Transport Variables in Cardiogenic Shock Secondary to Acute Myocardial Infarction, and Response to Treatment**

John E. Creamer, J. Denis Edwards, and Peter Nightingale

What are oxygen transport variables and how do they respond to treatment? We prospectively studied 19 patients and found that when cardiogenic shock responds to treatment, large increases in oxygen delivery lead to small increases in oxygen consumption but large increases in mixed venous oxygen saturation, reflecting improved tissue oxygen availability.

1301**Anatomic Validation of Electrocardiographic Estimation of the Size of Acute or Healed Myocardial Infarcts**

Dorina C. Sevilla, Nancy B. Wagner, Richard D. White, Steven L. Peck, Raymond E. Ideker, Donald B. Hackel, Keith A. Reimer, Ronald H. Selvester, and Galen S. Wagner

Seventeen new criteria added to the simplified version of the Selvester QRS scoring system to comprise the complete version were evaluated to determine their value in estimating the size of single infarcts. The study population was made up of 21 anterior, 30 inferior and 20 posterolateral single myocardial infarction patients with no evidence of bundle branch or fascicular blocks, ventricular hypertrophy or previous myocardial infarction on their final stable electrocardiogram. This study documents the improved ability provided by the 17 additional non-Q-wave criteria, which have been added in the complete version of this scoring system, regarding the sizing of infarcts in the region of the left ventricle supplied by the left circumflex artery.

1308**Comparison of the Effects of a Controlled-Release Formulation of Isosorbide-5-Mononitrate and Conventional Isosorbide Dinitrate on Exercise Performance in Men with Stable Angina Pectoris**

Ricardo Seabra-Gomes, Ana Maria Aleixo, Manuela Adao, Francisco Pereira Machado, Miguel Mendes, Guilherme Bruges, and Jose Luis Palos

We evaluated the exercise performance of 33 men with stable exertional angina pectoris in a randomized, double-blind, crossover study before and after 2 weeks' treatment with controlled-release isosorbide-5-mononitrate, 60 mg once daily, and conventional isosorbide dinitrate, 20 mg 3 times daily. Controlled-release isosorbide-5-mononitrate administered once daily appears to be as effective as conventional isosorbide dinitrate given 3 times daily in patients with stable angina pectoris.

1313**Clinical Significance of Silent Ischemia in Unstable Angina Pectoris**

Ian Wilcox, S. Ben Freedman, David T. Kelly, and Phillip J. Harris

We examined the clinical significance of transient myocardial ischemia during early Holter recordings in 66 medically treated patients with unstable angina. In these patients, only 20% of whom had reversible changes on 12-lead electrocardiograms during chest pain, recurrent rest pain (sensitivity 100%, specificity 49%) was a more clinically significant prognostic factor.

1317

Risk Stratification of Single or Double Vessel Coronary Artery Disease and Impaired Left Ventricular Function Using Exercise Radionuclide Angiography

Todd D. Miller, Charles P. Taliercio, Alan R. Zinsmeister, and Raymond J. Gibbons

Sixty-five patients with 1- or 2-vessel coronary artery disease and impaired left ventricular function at rest were followed for a median of 24 months. By regression analysis, a severely ischemic exercise radionuclide angiogram was the only variable predictive of event-free survival. This study demonstrates that exercise radionuclide angiography aids in the risk stratification of such patients and identifies a subgroup at high risk for future events.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1322

Usefulness of Head-up Tilt Test in Evaluating Patients with Syncope of Unknown Origin and Negative Electrophysiologic Study

Antonio Raviele, Gianni Gasparini, Francesco Di Pede, Pietro Delise, Aldo Bonso, and Eligio Piccolo

We used head-up tilt to 60° for 60 minutes to assess the possible vasovagal origin of syncope in 30 patients. The findings suggest that (1) head-up tilt is a useful test to unmask susceptibility to vasovagal reaction in patients with syncope of unknown origin; (2) withdrawal of α -sympathetic tone is the principal mechanism responsible for vasodilation and syncope during passive upright posture; and (3) α -adrenergic agonists may be of value in preventing spontaneous episodes of vasovagal syncope.

1328

Effectiveness of Propranolol Added to a Type I Antiarrhythmic Agent for Sustained Ventricular Tachycardia Secondary to Coronary Artery Disease

Ted D. Frierling, Hugh Lipshutz, Roger A. Marinchak, Jane L. Stohler, and Peter R. Kowey

The addition of propranolol to a type I antiarrhythmic drug was evaluated in 37 patients who had inducible ventricular tachycardia. During a 20-month mean follow-up, only 3 of 17 patients treated long-term died suddenly or had a recurrence of ventricular tachycardia. Thus, β blockade has measurable antiarrhythmic effects and can augment the effects of type I agents.

1334

Changes in Regional Adrenergic Tone During Sustained Ventricular Tachycardia Associated with Coronary Artery Disease or Idiopathic Dilated Cardiomyopathy

Kenneth A. Ellenbogen, Michael L. Smith, Marc D. Thames, and Pramod K. Mohanty

To determine the time course and magnitude of regional changes in α -adrenergic tone during ventricular tachycardia, we measured VT cycle length, arterial pressure, forearm blood flow and forearm vascular resistance in 15 patients. After VT was induced, mean forearm blood flow decreased and mean forearm vascular resistance increased. Most patients with symptomatic VT demonstrate sympathetic vasoconstriction and these changes are maximal during the first 30 seconds of VT.

1339

Usefulness of Disopyramide for Prevention of Upright Tilt-Induced Hypotension-Bradycardia

Simón Milstein, Jeffrey Buetikofer, Ann Dunnigan, David G. Benditt, Charles Gornick, and Walter J. Reyes

Susceptibility to neurally mediated hypotension-bradycardia has been attributed in part to accentuated afferent neural traffic arising from cardiopulmonary mechanoreceptors and, consequently, may be diminished by agents with anticholinergic and negative inotropic effects, such as disopyramide phosphate. Electrocardiographic and hemodynamic responses to upright tilt testing (alone or during isoproterenol infusion) before and after disopyramide therapy were evaluated in 10 patients with recurrent neurally mediated syncope. Data indicate that oral disopyramide may be effective for preventing neurally mediated syncope.

1345

Increased Vagal Cardiac Nerve Traffic Prolongs Ventricular Refractoriness in Patients Undergoing Electrophysiologic Testing

Kenneth A. Ellenbogen, Michael L. Smith, and Dwain L. Eckberg

We assessed the effect of enhanced vagal tone on sinus cycle length and right ventricular refractoriness in 26 patients using neck suction or phenylephrine infusion. Results show that vagal stimulation causes a small but significant increase in prolongation of right ventricular effective refractory period and functional refractory period. Thus, the potential benefits of enhanced vagal tone may not be directly mediated by effects on ventricular refractoriness.

1351

Circadian Variation in Ventricular Electrical Instability Associated with Coronary Artery Disease

James McClelland, Blair Halperin, Joel Cutler, Peter Kudenchuk, Jack Kron, and John McAnulty

A large series of ventricular stimulation studies was analyzed to determine whether circadian variation in ventricular electrical instability exists. Data indicate that the time of day during which ventricular stimulation tests are performed does not affect test results and therefore does not need to be controlled during electrophysiologic studies. If these data are parallel to those in ambulatory patients with coronary artery disease, then circadian changes in ventricular electrical instability may not play as important a role in the circadian pattern of sudden cardiac death as had been previously thought.

SYSTEMIC HYPERTENSION

1358

Validity of Arm Ergometer Blood Pressures Immediately After Exercise

Victoria Hollingsworth, Phillip Bendick, Barry Franklin, Seymour Gordon, and Gerald C. Timmis

We report a new method of assessing systolic blood pressure during arm-crank ergometry, using Doppler flowmeter techniques to measure the difference in ankle pressure at rest and during exercise. Our study compared estimated brachial systolic BP values during arm-crank ergometry with those obtained immediately after exercise by the standard cuff method. The findings indicate that systolic BPs taken by the standard cuff method are likely to underestimate the true physiologic response.

CONGESTIVE HEART FAILURE

1361

Hemodynamic Effects of Oral Nicorandil in Congestive Heart Failure

Frank D. Tice, Philip F. Binkley, Robert J. Cody, Melvin L. Moeschberger, J. Scott Mohrland, Daniel L. Wolf, and Carl V. Leier

Twenty-five patients with congestive heart failure underwent a double-blind, randomized study of the acute hemodynamic effects of orally administered nicorandil, a newly developed vasodilator drug; a dose range of 10 to 60 mg was studied. This study suggests that first-dose orally administered nicorandil elicits favorable but brief hemodynamic effects in congestive heart failure at doses ≥ 40 mg.

VALVULAR HEART DISEASE

1368

Saline Contrast Enhancement of Tricuspid Regurgitant Jets Detected by Doppler Color Flow Imaging

Alan D. Waggoner, Benico Barzilai, and Julio E. Pérez

Can intravenous injection of normal saline enhance imaging of tricuspid regurgitant jets using color flow Doppler? When the 4-chamber view was used and color gain settings were optimized, contrast enhancement led to a significant increase in TR jet area, length and ratio of jet area to right atrial area versus baseline. Contrast enhancement increases the amplitude of Doppler signals responsible for transvalvular and regurgitant flow.

1372

Preoperative Left and Right Ventricular Performance in Combined Aortic and Mitral Regurgitation and Comparison with Isolated Aortic or Mitral Regurgitation

Nathaniel Niles, Jeffrey S. Borer, Mazen Kamen, Clare Hochreiter, Richard B. Devereux, and Paul Kligfield

We determined preoperative radionuclide cineangiographic right ventricular and left ventricular ejection fraction at rest and during exercise, and resting echocardiographic indexes and hemodynamic and angiographic parameters in 8 symptomatic patients with severe, combined aortic and mitral regurgitation, and compared the results with those of 47 similarly symptomatic patients with isolated severe AR or MR. Data indicate that symptomatic operative candidates with AR/MR have poorer LV and RV performance than similarly symptomatic operative candidates with AR or MR alone.

CONGENITAL HEART DISEASE

1379

The "Laid-Back" Aortogram: An Improved Angiographic View for Demonstration of Coronary Arteries in Transposition of the Great Arteries

Valerie S. Mandell, James E. Lock, John E. Mayer, Ira A. Parness, and Thomas J. Kulik

Preoperative demonstration of coronary arterial anatomy may be important for babies with transposition of the great arteries or double-outlet right ventricle who are candidates for the arterial switch operation. An improved angiographic projection, in which the frontal x-ray tube is caudally angled, resulting in a "laid-back" position of the image intensifier and cine camera, provides superior visualization of the coronary arteries and their relation to the aorta and the pulmonary artery. This view is also easier to interpret than conventional projections.

1384

Usefulness of a Systemic Hypertension In-Hospital Educational Program

Robert A. González-Fernández, Mercedes Rivera, Dominga Torres, Joaquin Quiles, and Alma Jackson

To determine the short-term effects on compliance and blood pressure control of an in-hospital educational program, 47 patients with high BP were randomized to receive an educational program and questionnaire or questionnaire only. Eight weeks after the interventions, the compliance improved by 60% ($p = 0.04$) and the BP was effectively controlled ($p = 0.005$) in the patients who received the educational program. An in-hospital educational program in patients with high BP is effective in improving compliance and short-term BP control.

MISCELLANEOUS

1387

Doppler Echocardiographic Flow Velocity Measurements in the Superior Vena Cava During the Valsalva Maneuver in Normal Subjects

Aaron J. Gindea, James Slater, and Itzhak Kronzon

Superior vena cava Doppler echocardiography was performed during the Valsalva maneuver in 13 normal subjects. During strain, flow velocity increased and superior vena cava diameter decreased. One of the ways by which flow decreases during the Valsalva maneuver may be external compression of the superior vena cava by increased intrathoracic pressure.

METHODS

1392

Real-Time Intravascular Ultrasound Imaging in Humans

Natesa G. Pandian, Andreas Kreis, Andrew Weintraub, Amir Motarjeme, Mark Desnoyers, Jeffrey M. Isner, Marvin A. Konstam, Deeb N. Salem, and Vic Millen

We evaluated the feasibility of in vivo intraarterial ultrasound imaging in 26 patients. This new imaging approach has a number of potential applications in the diagnosis and treatment of arterial diseases.

EDITORIAL

1397

Suppression of Ventricular Arrhythmias by Magnesium

Dan Tzivoni and Andre Keren

BRIEF REPORTS

1400

Effects of Ventricular Pacing on Atrial Natriuretic Peptide Levels During Submaximal Exercise in Complete Atrioventricular Block

Cheuk-Kit Wong, Chu-Pak Lau, Chun-Ho Cheng, Wing-Hung Leung, Kin-Kee Pun, and M. Gary Nicholls

1402

HLA-A, B, DR, and DQ Antigens in Black Patients with Idiopathic Dilated Cardiomyopathy

Breminand Maharaj and Michael G. Hammond

1404

Positive Blood Cultures During Transesophageal Echocardiography

Günter Gorge, Raimund Erbel, Karl Jürgen Henrichs, Hans-Martin Wenchel, Heinz-Peter Werner, and Jürgen Meyer

CASE REPORT

1406

Asymptomatic Persistent Fifth Aortic Arch (Congenital Double-Lumen Aortic Arch) in an Adult

Tal Geva, Ronnie A. Ray, Francesco Santini, Stella Van Praagh, and Richard Van Praagh

FROM THE EDITOR

1408

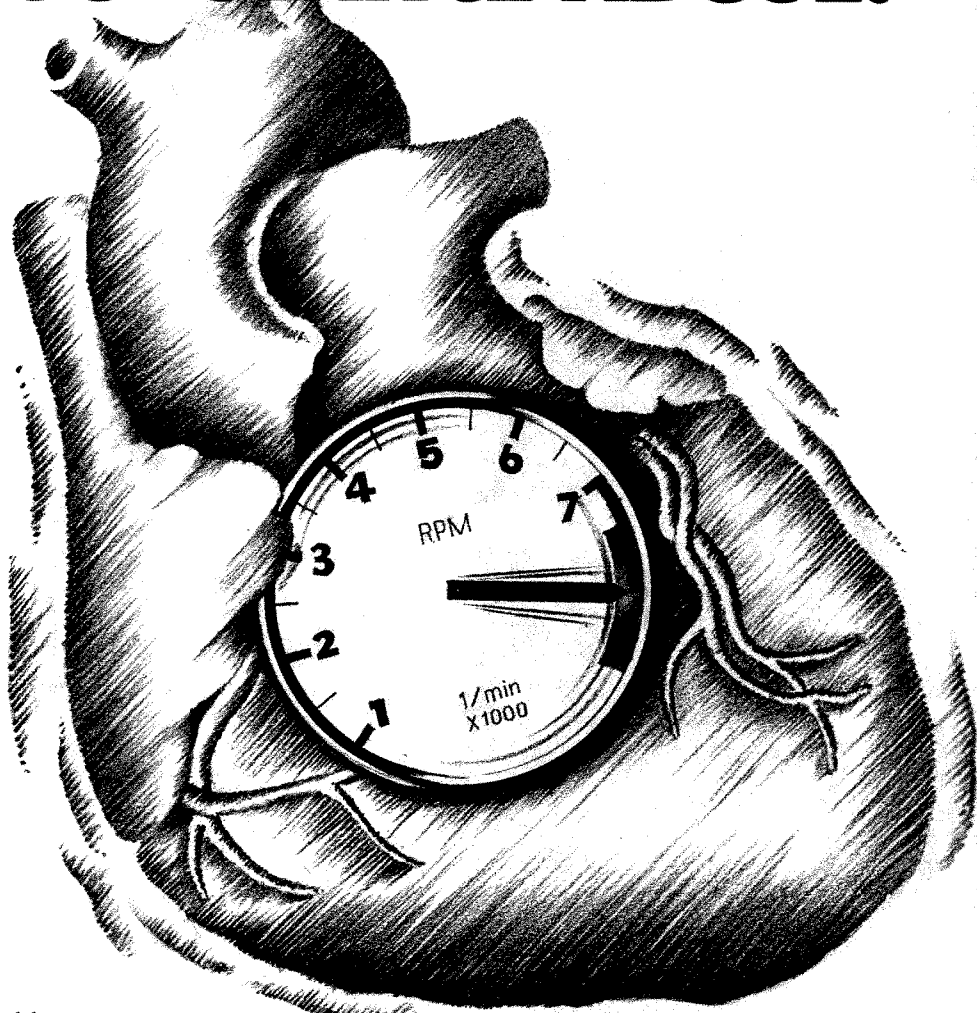
Making Clinical Studies Involving Many Patients Useful to the Single Patient

William C. Roberts

INSTRUCTIONS TO AUTHORS on page 1409

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CORONARY ARTERY DISEASE

1287**Propranolol-Induced Lipid Changes and Their Prognostic Significance After a Myocardial Infarction: The Beta-Blocker Heart Attack Trial Experience**

Robert P. Byington, Janine Worthy, Timothy Craven, and Curt D. Furberg

Concern continues to be expressed about the lipid-altering effects of long-term β -blocker use. Data collected for the Beta-Blocker Heart Attack Trial, the largest long-term clinical trial of a β blocker in postmyocardial infarction patients, have been analyzed to address this concern. By the 6-month postinfarction visit, propranolol was shown to raise triglyceride levels by an average of 35 mg/dl and lower high density lipoprotein by 3 mg/dl. However, in multivariate analyses adjusting for these changes, propranolol-induced beneficial reductions in mortality and morbidity remained on the order of 20%.

1292**Mechanism of Acute Myocardial Infarction in Patients with Prior Coronary Artery Bypass Grafting and Therapeutic Implications**

Cindy L. Grines, David C. Booth, Steven E. Nissen, John C. Gurley, Kim A. Bennett, William N. O'Connor, and Anthony N. DeMaria

Angiograms obtained between 1 hour and 7 days of acute myocardial infarction (median 1 day) were reviewed in 50 patients with prior coronary artery bypass grafting. The vein graft was identified as the infarct vessel in 38 (76%) patients and contained extensive thrombus. Successful reperfusion occurred in only 2 of 8 (25%) grafts after intravenous thrombolytic therapy while intragraft thrombolysis with or without additional angioplasty was successful in 8 of 10 (80%) grafts. Thus, in this population, acute myocardial infarction is usually caused by thrombotic occlusion of a saphenous vein graft. Restoration of flow in the graft may require subselective drug infusion, a higher thrombolytic dose or angioplasty.

Continued on page A17

1297

Hemodynamic and Oxygen Transport Variables in Cardiogenic Shock Secondary to Acute Myocardial Infarction, and Response to Treatment

John E. Creamer, J. Denis Edwards, and Peter Nightingale

We prospectively studied 19 patients with clinical cardiogenic shock after acute myocardial infarction to determine oxygen transport variables and their response to treatment. Femoral and pulmonary arterial catheters were inserted before any therapy except correction of hypoxemia, defibrillation or pacing. In 3 patients mean arterial pressure was >80 mm Hg and cardiac index >2.1 liters/min/m² with normal mixed venous oxygen saturation despite simultaneous clinical features of shock. They recovered with no further treatment. The other 16 patients were treated with intravenous fluids and dobutamine (37 ± 25 μ g/kg/min). Mean cardiac index increased from 1.3 ± 0.4 to 2.5 ± 0.4 liters/min/m² ($p < 0.001$). Mean oxygen delivery (DO_2) increased from 222 ± 65 to 384 ± 94 ml/min/m² ($p < 0.001$), and mean oxygen consumption (VO_2) from 104 ± 32 to 125 ± 24 ml/min/m² ($p < 0.05$). VO_2 was maintained even when DO_2 was <330 ml/min/m². Mean mixed venous oxygen saturation increased from 52 ± 14 to $68 \pm 8\%$ ($p < 0.001$) and mean oxygen extraction ratio decreased from 50 ± 15 to $32 \pm 6\%$ ($p < 0.001$). Thirteen patients survived.

1301

Anatomic Validation of Electrocardiographic Estimation of the Size of Acute or Healed Myocardial Infarcts

Dorina C. Sevilla, Nancy B. Wagner, Richard D. White, Steven L. Peck, Raymond E. Ideker, Donald B. Hackel, Keith A. Reimer, Ronald H. Selvester, and Galen S. Wagner

The 17 new criteria added to the simplified version of the Selvester QRS scoring system to comprise the complete version were evaluated to determine their value in estimating the size of single infarcts. These non-Q-wave criteria might be particularly useful regarding posterolateral infarcts in the distribution of the left circumflex artery. Seventy-one patients grouped into those with single infarcts in each of the 3 major coronary artery distributions of the left ventricle were included. The complete version indicated a mean electrocardiographic infarct size that better approximated the anatomic size in all locations. However, the correlation between anatomic and electrocardiographic infarct size was particularly improved for the posterolateral group from $r = 0.55$ ($p < 0.01$) to $r = 0.70$ ($p < 0.0006$).

1308

Comparison of the Effects of a Controlled-Release Formulation of Isosorbide-5-Mononitrate and Conventional Isosorbide Dinitrate on Exercise Performance in Men with Stable Angina Pectoris

Ricardo Seabra-Gomes, Ana Maria Aleixo, Manuela Adao, Francisco Pereira Machado, Miguel Mendes, Guilherme Bruges, and Jose Luis Palos

In a randomized, double-blind, crossover study, the exercise performance of 33 men with stable exertional angina pectoris was evaluated before and after 2 weeks' treatment with controlled-release isosorbide-5-mononitrate 60 mg once daily and conventional isosorbide dinitrate 20 mg 3 times daily. Both drugs exhibited significant antianginal efficacy as estimated by total exercise time and the time to onset of chest pain and there was no evidence for the development of tolerance. During treatment with controlled-release isosorbide-5-mononitrate, there were significantly fewer signs of myocardial ischemia and it was associated with less severe headache. Controlled-release isosorbide-5-mononitrate administered once daily appears to be as effective as conventional isosorbide dinitrate given 3 times daily in patients with stable angina pectoris.

1313

Clinical Significance of Silent Ischemia in Unstable Angina Pectoris

Ian Wilcox, S. Ben Freedman, David T. Kelly, and Phillip J. Harris

We examined the clinical significance of transient myocardial ischemia during early Holter recordings in 66 medically treated patients with unstable angina. Ischemic ST-segment changes occurred in only 11% and, although predominantly silent (70%), few patients (3%) had exclusively silent episodes. Although transient electrocardiographic changes during Holter monitoring were a highly specific (92%) predictor of subsequent death or nonfatal myocardial infarction, the sensitivity was low (25%). In these patients, only 20% of whom had reversible changes on 12-lead electrocardiograms during chest pain, recurrent rest pain (sensitivity 100%, specificity 49%) was a more clinically significant prognostic factor.

1317

Risk Stratification of Single or Double Vessel Coronary Artery Disease and Impaired Left Ventricular Function Using Exercise Radionuclide Angiography

Todd D. Miller, Charles P. Taliercio, Alan R. Zinsmeister, and Raymond J. Gibbons

Sixty-five patients with 1- or 2-vessel coronary artery disease (CAD) and left ventricular (LV) ejection fraction <50% were followed for a median duration of 24 months. Eleven patients (17%) had severely ischemic exercise radionuclide angiograms, defined as: decrease in ejection fraction with exercise; ≥ 1 mm of ST-segment depression; and peak exercise workload ≤ 600 kg-m/min. Eleven patients experienced initial significant car-

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ACTIVASE®

ALTEPLASE, RECOMBINANT

A TISSUE PLASMINOGEN ACTIVATOR

Brief Summary

Consult full prescribing information before using.

INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

PRECAUTIONS: General Standard management of MI should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE®. If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >25 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

Total Dose ≤ 100 mg		Total Dose > 100 mg	
gastrointestinal	5%		5%
genitourinary	4%		4%
ecchymosis	1%		<1%
retroperitoneal	<1%		<1%
epistaxis	<1%		<1%
gingival	<1%		<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE®, Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-14 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials¹⁻⁷ is not significantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites. **Allergic Reactions** No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: Administer ACTIVASE® as soon as possible after the onset of symptoms.

ACTIVASE® is for intravenous administration only.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.⁸

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution. **No other medication should be added to infusion solutions containing ACTIVASE®.** Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

ACTIVASE® Alteplase, recombinant

Manufactured by

GENENTECH® INC.

460 Point San Bruno Blvd.

South San Francisco, CA 94080

April, 1989

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diac events during follow-up: 4 cardiac deaths, 1 cardiac arrest, 4 myocardial infarctions and 2 bypass or angioplasty procedures ≥ 3 months after the exercise radionuclide angiogram. Four of 11 patients (36%) with severely ischemic exercise studies versus 7 of 54 patients (13%) without ischemia had events. Event-free survival at 18 months was 73% for patients with severe exercise ischemia versus 92% for those without ischemia ($p < 0.05$). Thus, a severely ischemic exercise radionuclide angiogram identifies patients with 1- or 2-vessel CAD and impaired resting LV function at high risk for subsequent cardiac events.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1322

Usefulness of Head-up Tilt Test in Evaluating Patients with Syncope of Unknown Origin and Negative Electrophysiologic Study

Antonio Raviele, Gianni Gasparini, Francesco Di Pede, Pietro Delise, Aldo Bonso, and Eligio Piccolo

Head-up tilt to 60° for 60 minutes was used to assess the possible vasovagal origin of loss of consciousness in 30 patients with syncope that remained unexplained at the end of electrophysiologic study. Syncope was reproduced in association with hypotension alone or hypotension and bradycardia in 15 patients (50%). Pharmacologic tests were performed in 9 of these patients with reproducible baseline positive tests. Atropine prevented tilt-induced syncope in 33% of the cases, propranolol in 25% and etilephrine in all. None of the 6 patients treated on a long-term basis with etilephrine had syncopal recurrences during a mean follow-up of 12 months. The findings suggest that (1) head-up tilt is a useful test to unmask susceptibility to vasovagal reaction in patients with syncope of unknown origin; (2) withdrawal of α -sympathetic tone is the principal mechanism responsible for vasodilation and syncope during passive upright posture; and (3) α -adrenergic agonists may be of value in preventing spontaneous episodes of vasovagal syncope.

1328

Effectiveness of Propranolol Added to a Type I Antiarrhythmic Agent for Sustained Ventricular Tachycardia Secondary to Coronary Artery Disease

Ted D. Friehling, Hugh Lipshutz, Roger A. Marinchak, Jane L. Stohler, and Peter R. Kowey

The addition of propranolol to a type I antiarrhythmic drug was evaluated in 37 patients who had inducible ventricular tachycardia (VT). In the first group of 23 patients, intravenous propranolol was added to a type I drug that had not prevented induction of VT. Propranolol increased the mean ventricular effective refractory period, increased VT cycle length in 10 and rendered 7 patients noninducible. In the other 14 patients, intravenous propranolol was infused first and testing was repeated. If VT remained inducible, a type I drug was added. Propranolol increased the effective

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refractory period and mean VT cycle length. In 7 patients, VT could not be reinitiated (3 with propranolol alone and 4 with the combination). Seventeen patients were discharged receiving propranolol alone (3) or an effective combination (14). During a 20-month mean follow-up, only 3 patients died suddenly or had a recurrence of VT. Thus, β blockade has measurable antiarrhythmic effects and can augment the effect of type I agents.

1334

Changes in Regional Adrenergic Tone During Sustained Ventricular Tachycardia Associated with Coronary Artery Disease or Idiopathic Dilated Cardiomyopathy

Kenneth A. Ellenbogen, Michael L. Smith, Marc D. Thames, and Pramod K. Mohanty

The hemodynamic tolerance to an episode of ventricular tachycardia (VT) varies widely. Little is known about the factors responsible for these different responses. We measured VT cycle length, arterial pressure, forearm blood flow and forearm vascular resistance by venous occlusion plethysmography to determine the time course and magnitude of regional changes in α -adrenergic tone during VT in 15 patients. After the induction of VT, mean forearm blood flow decreased from 3.2 ± 1.1 to 2.2 ± 0.8 ml/min/100 ml ($p = 0.0002$) and the mean forearm vascular resistance increased from 32 ± 14 to 40 ± 14 units ($p = 0.01$). There was no significant difference between forearm vascular resistance in the first and last 30 seconds of VT. After the infusion of intraarterial phentolamine, vasoconstriction during VT was reduced by 60 to 70%. We conclude that patients with symptomatic VT demonstrate sympathetic vasoconstriction that is rapid in onset and is due to stimulation of α adrenoreceptors.

1339

Usefulness of Disopyramide for Prevention of Upright Tilt-Induced Hypotension-Bradycardia

Simón Milstein, Jeffrey Buetikofer, Ann Dunnigan, David G. Benditt, Charles Gornick, and Walter J. Reyes

Susceptibility to neurally mediated hypotension-bradycardia has been attributed in part to accentuated afferent neural traffic arising from cardiopulmonary mechanoreceptors and, consequently, may be diminished by agents with anticholinergic and negative inotropic effects, such as disopyramide phosphate. Electrocardiographic and hemodynamic responses to upright tilt testing (alone or during isoproterenol infusion) before and after disopyramide therapy were evaluated in 10 patients with recurrent neurally mediated syncope. Untreated syncope was reproduced during upright tilt testing and was associated with significant hypotension and inappropriate heart rate slowing. After oral disopyramide (mean plasma level 3.0 ± 0.64 μ g/ml), all patients tolerated tilt without symptoms, hypotension or bradycardia. During subsequent 20 ± 5 months of follow-up on disopyramide therapy, all but 1 patient remain asymptomatic. Thus, oral disopyramide may be effective for preventing neurally mediated syncope.

1345

Increased Vagal Cardiac Nerve Traffic Prolongs Ventricular Refractoriness in Patients Undergoing Electrophysiologic Testing

Kenneth A. Ellenbogen, Michael L. Smith, and Dwain L. Eckberg

We assessed the effects of enhanced vagal tone (-60 mm Hg neck suction or phenylephrine infusion) on sinus cycle length and right ventricular refractoriness in 26 patients. Neck suction prolonged sinus cycle length (146 ± 20 ms) and right ventricular effective refractory period (4 ± 1 ms) and functional refractory period (5 ± 1 ms) ($p < 0.0002$ for each). Mean change in effective refractory period and functional refractory period correlated significantly with the peak change in sinus cycle length during neck suction ($r = 0.46$ and $r = 0.58$). Phenylephrine infusion also significantly increased effective refractory period (5 ± 2 ms) and functional refractory period (10 ± 3 ms). These data show that vagal stimulation causes a small but significant prolongation of right ventricular effective refractory period and functional refractory period. Hence, potential benefits of enhanced vagal tone may not be directly mediated by effects on ventricular refractoriness.

1351

Circadian Variation in Ventricular Electrical Instability Associated with Coronary Artery Disease

James McClelland, Blair Halperin, Joel Cutler, Peter Kudenchuk, Jack Kron, and John McAnulty

Although sudden cardiac deaths and ischemic cardiac events clearly occur in a circadian pattern, no such pattern has been shown for primary arrhythmic events or ventricular electrical instability. We investigated if circadian variation in ventricular electrical instability exists by analyzing results of 2 drug-free ventricular stimulation studies in each of 162 patients with coronary artery disease. Rate and duration of induced arrhythmia, number of extrastimuli required to induce arrhythmia and changes in these factors between the 2 tests in each patient were analyzed. No significant circadian variation was found in any measure of ventricular electrical instability. These findings show that the time of day during which ventricular stimulation tests are performed does not affect test results and therefore does not need to be controlled during electrophysiologic studies. In addition, we speculate that if ventricular electrical instability in this group is parallel to that of ambulatory subjects, circadian variation in ventricular electrical instability may not play as important a role as previously thought in the circadian pattern of sudden death.

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SYSTEMIC HYPERTENSION

1358

Validity of Arm Ergometer Blood Pressures Immediately After Exercise

Victoria Hollingsworth, Phillip Bendick, Barry Franklin, Seymour Gordon, and Gerald C. Timmis

To assess the validity of blood pressure (BP) measured by the standard cuff method immediately after (within 15 seconds) upper body exercise, we studied 18 healthy men (mean age 32 years) who completed 3 progressive workloads during arm-crank ergometry. Ankle systolic BP was measured at the dorsalis pedis artery at seated rest, 15 seconds before completion of each exercise stage and immediately after each workload, using a Doppler stethoscope; simultaneous postexercise brachial systolic BPs were determined by auscultation. Brachial systolic BP during arm-crank ergometry was estimated using the increase in ankle systolic BP. Brachial systolic BPs, obtained immediately after arm-crank ergometry, were significantly lower than those estimated during exercise ($p < 0.001$), with corresponding mean differences of 12, 29 and 31 mm Hg at 150, 300 and 450 $\text{kg} \cdot \text{m} \cdot \text{min}^{-1}$, respectively. These findings indicate that systolic BPs taken by the standard cuff method immediately after arm-crank ergometry are likely to underestimate "true" physiologic responses.

CONGESTIVE HEART FAILURE

1361

Hemodynamic Effects of Oral Nicorandil in Congestive Heart Failure

Frank D. Tice, Philip F. Binkley, Robert J. Cody, Melvin L. Moeschberger, J. Scott Mohrland, Daniel L. Wolf, and Carl V. Leier

The acute hemodynamic response to a single oral dose of nicorandil was invasively measured in 25 patients with chronic congestive heart failure. Using a blinded, placebo-controlled design, a dose range of 10 to 60 mg was studied. Nicorandil, at doses ≥ 40 mg, produced statistically significant and favorable hemodynamic effects. However, the duration of action was relatively brief (most hemodynamic parameters returned close to baseline within 3 hours), with loss of activity occurring in concert with a rapid decrease in plasma concentration.

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“IABP to

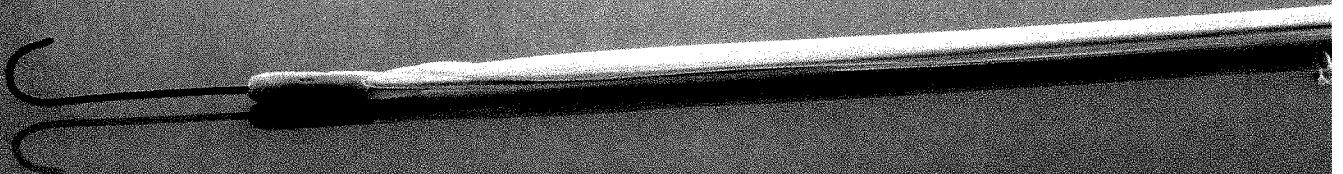
Datascope's continued innovative development of percutaneous catheters and intra-aortic balloon pumps has greatly expanded the use of IABP to relieve ischemic pain, prevent shock and decrease the extent and severity of ischemic injury.

It is commonly accepted that intra-aortic balloon pumping is the treatment of choice in critical situations, where IABP can produce dramatic, lifesaving results.

However, with our recent developments in balloon and pump technology, institution of circulatory support is now simplified. Insertion of the balloon can be accomplished in 5 to 10 minutes, with reduced incidence of circulatory complications.

Therefore the procedure is now being used prophylactically, with excellent results, in a larger number of non-life-threatening situations.

The intra-aortic balloon pump is playing a critical role by relieving refractory anginal pain and stabilizing many patients.



VALVULAR HEART DISEASE

1368

Saline Contrast Enhancement of Tricuspid Regurgitant Jets Detected by Doppler Color Flow Imaging

Alan D. Waggoner, Benico Barzilai, and Julio E. Pérez

Saline contrast enhancement was performed in 29 patients with tricuspid regurgitation (TR) detected by either transthoracic (25) or transesophageal (4) color flow imaging. When the 4-chamber view was used and color gain settings were optimized, contrast enhancement led to a significant increase ($p < 0.0001$) in TR jet area, length and ratio of jet area to right atrial area from baseline values. The increases in color flow-imaged tricuspid jet area and length were not associated with changes in TR jet or diastolic inflow velocities measured by continuous wave Doppler at baseline and after contrast enhancement. This technique improves delineation of the color flow-imaged TR jet, reduces the effect of attenuation and improves signal to noise ratio.

1372

Preoperative Left and Right Ventricular Performance in Combined Aortic and Mitral Regurgitation and Comparison with Isolated Aortic or Mitral Regurgitation

Nathaniel Niles, Jeffrey S. Borer, Mazen Kamen, Clare Hochreiter, Richard B. Devereux, and Paul Kligfield

Preoperative right (RV) and left ventricular (LV) performance in operative candidates with severe, combined aortic and mitral regurgitation (AR/MR) has not been well defined. We determined preoperative radionuclide cineangiographic RV and LV ejection fraction at rest and during exercise, resting echocardiographic indexes and hemodynamic and angiographic parameters in 8 symptomatic patients with AR/MR and compared the results with those of 47 similarly symptomatic patients with isolated severe AR or MR. Before operation, symptomatic patients with AR/MR had significantly lower LV ejection fraction than patients with MR ($p < 0.025$) and tended to have lower LV ejection fraction than patients with AR (difference not significant). RV ejection fraction at rest was lower in AR/MR than in AR ($p < 0.01$) and tended to be lower than in MR (difference not significant). At average postoperative follow-up of 72 to 76 months (survivors in each group), symptomatic patients with AR/MR had significantly poorer survival than symptomatic patients with MR ($p < 0.05$), and significantly more residual symptoms than patients with AR ($p < 0.05$). Our findings suggest that symptomatic operative candidates with AR/MR have poorer LV and RV performance than similarly symptomatic operative candidates with AR or MR alone. This finding may help to explain poorer postoperative results in the AR/MR group.

CONGENITAL HEART DISEASE

1379

The "Laid-Back" Aortogram: An Improved Angiographic View for Demonstration of Coronary Arteries in Transposition of the Great Arteries

Valerie S. Mandell, James E. Lock, John E. Mayer, Ira A. Parness, and Thomas J. Kulik

Preoperative demonstration of coronary arterial anatomy may be important for babies with transposition of the great arteries or double-outlet right ventricle who are candidates for the arterial switch operation. An improved angiographic projection, in which the frontal x-ray tube is caudally angled, resulting in a "laid-back" position of the image intensifier and cine camera, provides superior visualization of the coronary arteries and their relation to the aorta and the pulmonary artery. This view is also easier to interpret than conventional projections, which is an important advantage.

1384

Usefulness of a Systemic Hypertension In-Hospital Educational Program

Robert A. González-Fernández, Mercedes Rivera, Dominga Torres, Joaquin Quiles, and Alma Jackson

To determine the short-term effects on compliance and blood pressure (BP) control of an in-hospital educational program, 47 patients with high BP were randomized to receive an educational program and questionnaire or questionnaire only. Eight weeks after the interventions, the compliance improved 60% ($p = 0.04$) and the BP was effectively controlled ($p = 0.005$) in the patients who received the educational program. An in-hospital educational program in patients with high BP is effective in improving compliance and short-term BP control.

MISCELLANEOUS

1387

Doppler Echocardiographic Flow Velocity Measurements in the Superior Vena Cava During the Valsalva Maneuver in Normal Subjects

Aaron J. Gindea, James Slater, and Itzhak Kronzon

Doppler echocardiography was performed during the Valsalva maneuver in 13 normal subjects. Superior vena cava flow velocities and flow velocity integrals were measured in all 13 subjects. In the 5 subjects in whom the superior vena cava was clearly visualized throughout the maneuver, vena cava diameter was also analyzed. The superior vena cava flow velocity integral at rest was 17 ± 2 cm. It diminished significantly, disappeared or reversed (-13 ± 6 cm, $p < 0.001$) with phase I of the maneuver. During

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Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP $\geq$ 180 mm Hg and/or diastolic BP $\geq$ 110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

PRECAUTIONS: **General** Standard management of MI should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE®. If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose $\leq$ 100 mg	Total Dose $>$ 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	$<1\%$
retroperitoneal	$<1\%$	$<1\%$
epistaxis	$<1\%$	$<1\%$
gingival	$<1\%$	$<1\%$

The incidence of intracranial bleeding in patients treated with ACTIVASE® Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials¹⁻⁷ is not significantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) ($p = 0.26$).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites. **Allergic Reactions** No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: Administer ACTIVASE® as soon as possible after the onset of symptoms.

ACTIVASE® is for intravenous administration only.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.⁸

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 10 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution. **No other medication should be added to infusion solutions containing ACTIVASE®.** Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

ACTIVASE® Alteplase, recombinant

Manufactured by

GENENTECH, INC.

460 Point San Bruno Blvd.

South San Francisco, CA 94080

April, 1989

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the maintenance phase (phase II), the flow velocity integral increased significantly (31 ± 2 cm, $p = 0.05$ vs baseline and phase I) and was associated with a decrease in superior vena cava lumen diameter at the time of Valsalva and continuing throughout the strain. With release of the maneuver (phase III), there was a sudden significant increase in flow velocity integral (61 ± 2 cm, $p = 0.005$ vs phase II) and superior vena cava lumen diameter. Subsequently, superior vena cava flow velocity integral returned to baseline values. This study suggests that one of the ways in which the Valsalva maneuver leads to decreased venous return may be by direct external compression of the superior vena cava.

METHODS**1392****Real-Time Intravascular Ultrasound Imaging in Humans**

Natesa G. Pandian, Andreas Kreis, Andrew Weintraub, Amir Motarjeme, Mark Desnoyers, Jeffrey M. Isner, Marvin A. Konstam, Deeb N. Salem, and Vic Millen

We evaluated the feasibility of in vivo intraarterial ultrasound imaging in 26 patients. After diagnostic cardiac catheterization or iliofemoral arteriography, 1 of 3 different models of 20-MHz ultrasound catheters was advanced retrograde into the iliac arteries or antegrade into the femoral arteries under fluoroscopy. In all patients we were able to obtain dynamic, 2-dimensional, cross-sectional arterial images. Normal arteries appeared circular with crisply defined lumens and pulsatile walls. The arterial walls presented a 3-layered appearance. Nonobstructive calcific plaques and obstructive arterial lesions were easily seen in the ultrasound images. In diseased arteries, the lumen had irregular shape bordered by thickened adynamic walls. While lumen size and abnormalities in arterial walls were easily identified, assessment of wall thickness was difficult. There were no complications. This study demonstrates the feasibility of intravascular ultrasound imaging in conscious humans and the ability to detect arterial disease. This new imaging approach has a number of potential applications in the diagnosis and treatment of arterial diseases.

EDITORIAL**1397****Suppression of Ventricular Arrhythmias by Magnesium**

Dan Tzivoni and Andre Keren

Continued on page A50

1990 NUTRITION UPDATE: YOUR PATIENTS' GUIDE TO WEIGHT LOSS AND GOOD HEALTH

Dear Doctor:

As you know, eating right, losing weight and keeping it off is vital to your patients' good health. According to leading dietitians, the American Heart Association and the American Cancer Society, a healthy diet should be calorie controlled, low in fat, low in cholesterol, high in fiber, high in carbohydrates and high in essential nutrients.

The Ultra Slim•Fast Weight Loss Program follows these accepted nutritional guidelines. Ultra Slim•Fast is not a liquid diet, but a well balanced nutritional program that recommends approximately 1200 calories per day. Three Ultra Slim•Fast shakes, one for breakfast, one for lunch, one for a snack and then a well balanced dinner will provide your patients with the balanced nutrition needed for good health.

Ultra Slim•Fast shakes are:

- delicious tasting, low in calories
- nutritionally fortified, high in fiber
- very low in fat, low in cholesterol



Breakfast . . .



Lunch . . .



Snack . . .



Dinner . . .

Anyone who wants to lose more than 50 pounds or more than 20% of their starting weight, should be monitored by a physician when using any weight loss program. In addition, very rapid weight loss can cause health problems. If your patients are losing more than two pounds a week (after the first week), encourage them to increase their caloric intake by drinking additional shakes or eating more food. Each can comes with menu suggestions that will educate your patients in choosing healthy, nutritious foods.

Millions of Americans are losing weight and keeping it off with Ultra Slim•Fast!

Ultra Slim•Fast is fast becoming the most popular weight loss program in America:

- Last year alone, more than 1 Billion Slim•Fast shakes were consumed.
- In 1990 this trend is continuing, a testament to the efficacy and success of this program.
- People continue to use Ultra Slim•Fast, even after they have lost weight, as a low fat breakfast, lunch or satisfying snack and find that it helps them keep the weight off.

Let us introduce you to Ultra Slim•Fast

Because we are confident that you, your family and your staff will enjoy using Ultra Slim•Fast, we want to send a free supply to your office and your home. We will include an Ultra Slim•Fast shaker and background material. Just let us know you are interested by completing the attached coupon.

FREE

Your personal supply FREE! . . . Ultra Slim•Fast

Mail to: Slim•Fast Foods, 145 East 57th Street, Suite 700, New York, N.Y. 10022

Please send a **free** 15oz. can of Ultra Slim•Fast and a shaker to my office and/or home.

Please stamp, label or print. Please do not use a P.O. Box.

MD ☐

DO ☐

Name _____ Medical Specialty _____

Address _____

City _____ State _____ Zip Code _____

My home address is:

Name _____

Address _____

City _____ State _____ Zip Code _____

BRIEF REPORTS

1400

Effects of Ventricular Pacing on Atrial Natriuretic Peptide Levels During Submaximal Exercise in Complete Atrioventricular Block

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FROM THE EDITOR

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Making Clinical Studies Involving Many Patients Useful to the Single Patient

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Propranolol-Induced Lipid Changes and Their Prognostic Significance After a Myocardial Infarction: The Beta-Blocker Heart Attack Trial Experience

Robert P. Byington, PhD, Janine Worthy, MSPH, Timothy Craven, MSPH, and Curt D. Furberg, MD, PhD

Beta blockers represent the only documented effective long-term prophylactic treatment for patients after myocardial infarction (MI). Concern continues to be expressed about the lipid-altering effects of their long-term use, especially β blockers without intrinsic sympathomimetic activity such as propranolol. Data collected for the Beta-Blocker Heart Attack Trial, the largest long-term clinical trial of β -blocker use in patients after MI, have been analyzed to address the following questions. To what extent does propranolol alter lipid levels at least 6 months after MI and initiation of therapy? How predictive of subsequent coronary events and mortality are lipid levels 6 months after MI? Is there any evidence that altered lipid levels attenuate any of the beneficial effect of propranolol on coronary morbidity and mortality? By the 6-month post-MI visit, propranolol was shown to raise serum triglyceride levels by about 17% (≈ 35 mg/dl) and lower serum high density lipoprotein (HDL) cholesterol by about 6% (≈ 3 mg/dl). There was no effect on total cholesterol or low density lipoprotein cholesterol. In other analyses, no lipid measured 6 months after the MI was strongly predictive of subsequent coronary events or mortality. For example, every 1-mg-lower HDL value was associated with only a 0.7% relative increase in the mortality rate. Theoretically, the estimated relative increase on all-cause mortality associated with propranolol-induced HDL reduction is about 2%. In multivariate analyses adjusting for changes in HDL and serum triglyceride, propranolol-induced beneficial reductions in mortality and morbidity remained on the order of 20%, 10 times the estimated hazard.

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Data from clinical trials have provided overwhelming scientific evidence that β -blocker therapy, whether administered acutely or over the long-term, reduces all-cause mortality and fatal or nonfatal coronary events in patients after myocardial infarction (MI).¹⁻³ In fact, β blockers are now the only documented long-term effective prophylactic treatment for MI patients.⁴ However, some concern continues to be expressed about the lipid-altering effects of long-term β -blocker use.⁵ Beta blockers without intrinsic sympathomimetic activity, such as propranolol, are associated with an increase in serum triglyceride levels and a decrease in serum high density lipoprotein (HDL) cholesterol levels, both of which are either thought or known to be associated with the development of coronary artery disease.^{6,7}

Most of the studies that have examined lipid changes associated with β -blocker use have focused on hypertensive or angina patients. The post-MI population poses special questions because their risk factors for subsequent events are different compared to the risk factors for pre-MI patients. Data collected for the Beta-Blocker Heart Attack Trial, the largest long-term clinical trial of β -blocker use in post-MI patients, have been analyzed to address the following questions. To what extent does propranolol alter lipid levels 6 and 12 months after an MI and the initiation of therapy? How predictive of subsequent coronary events and mortality (used as a surrogate measure of atherosclerosis) are lipid levels obtained 6 months after an MI? Is there any evidence that altered lipid levels attenuate any of the beneficial effect of propranolol on coronary morbidity and mortality?

METHODS

Study population: The Beta-Blocker Heart Attack Trial was a multicenter, placebo-controlled, randomized, double-blind clinical trial of the long-term administration of propranolol given to patients who had had a documented MI within the previous 5 to 21 days.^{8,9} Recruitment for the trial was conducted between June 1978 and October 1980, and the trial was terminated in October 1981. A total of 3,837 patients were randomized (1,916 into the propranolol group and 1,921 into

TABLE I Treatment Group Differences in Mean Values of Lipid Values over Time

Serum Lipid (mg/dl)	Clinic Visit	Propranolol		Placebo		Z of Difference
		Mean	No.	Mean	No.	
Total	Baseline	222.2	1,834	222.5	1,849	0.15
Cholesterol	6 months	260.0	1,577	258.6	1,585	-0.74
	12 months	260.4	1,645	260.2	1,602	-0.09
Triglyceride	Baseline	186.5	1,830	186.1	1,852	-0.12
	6 months	240.4	1,575	204.2	1,586	-7.06
	12 months	238.7	1,640	204.5	1,605	-6.46
HDL	Baseline	35.5	1,832	35.4	1,850	-0.38
	6 months	41.8	1,581	44.4	1,580	6.47
	12 months	42.2	1,645	45.2	1,601	7.24
Estimated LDL	Baseline	148.5	1,738	148.6	1,746	0.05
	6 months	173.1	1,328	175.0	1,393	1.08
	12 months	174.5	1,383	175.8	1,419	0.72

HDL = high density lipoprotein; LDL = low density lipoprotein.

the placebo group) in 30 clinical centers in the United States and 1 center in Canada. Men and women, aged 30 to 69 years, were eligible. Potential trial participants were excluded if they had medical contraindications to propranolol (such as severe congestive heart failure) or were already taking or were likely to be prescribed a β blocker.

On the basis of serum propranolol levels determined after 6 doses, propranolol patients were assigned to either a 60 mg 3 times daily or a 80 mg 3 times daily treatment program at 1 month after randomization. To maintain the double-blind nature of this trial, a comparable proportion of placebo patients had their doses "raised."¹⁰

Eligible subjects were followed for 12 to 40 months (mean 25). The primary endpoint for the trial was all-cause mortality, although cause-specific mortality was recorded as well as the occurrence of nonfatal recurrent MI. The major conclusions of the trial were that propranolol reduces mortality and the combined fatal/nonfatal coronary event rate.^{8,9} A detailed description of the design for this trial may be found elsewhere.¹¹

Lipid analytical methods: A special ancillary study was conducted during the trial to examine the change in lipid levels associated with propranolol use. The results have been previously reported.¹² For this study, lipid levels were measured at baseline, and at the 6- and 12-month follow-up visits. Venous blood was collected in the clinical centers, and serum was separated by low-speed centrifugation and frozen until analyses were centrally performed within 6 weeks. The serum was analyzed at the Miriam Hospital, Providence, Rhode Island.

Serum cholesterol and triglyceride concentrations were determined on a Gilford System 3500 computer-directed analyzer using enzymatic methods.^{13,14} Serum HDL values were estimated using techniques identical to those of the Lipid Research Clinics Program,¹⁵ except that the isopropanol and zeolite extraction steps were not required with the enzymatic methods. Serum low density lipoprotein (LDL) cholesterol was estimated using the Friedewald formula,¹⁶ i.e., $LDL = \text{total serum cholesterol} - (\text{serum HDL} + \text{serum triglyceride}/5)$.

Patients with a serum triglyceride value >400 mg/dl did not have their LDL estimated, and are excluded from these analyses.

Statistical analysis: The 4 serum lipids discussed herein are total serum cholesterol, serum triglyceride, serum HDL and the estimated serum LDL, obtained at baseline, 6 months and 12 months after randomization. The endpoints are observed rates of fatal or nonfatal coronary disease and all-cause mortality. Specifically, only those events that occurred after 6 months of treatment are presented (range of follow-up for these events 1 to 34 months; mean 19.4). Simple means, event rates and relative risks were calculated, as were Z scores for the differences in the means and rates.¹⁷ Cox regression techniques¹⁸ were used for the univariate and multivariate prediction of the occurrence of a fatal or nonfatal coronary event and all-cause mortality. For the multivariate analyses presented here, the following were used as covariates: 6-month lipid levels, change in lipid levels from baseline to the 6-month visit and treatment group assignment.

Because over 200 comparisons were made during the course of this analysis of the correlations among treatment group assignment, lipid levels and occurrence of endpoints, no formal tests for statistical significance were performed. The Z scores and relative risks that are presented may be used as guides to the magnitudes of the observed associations.¹⁹

RESULTS

Propranolol-induced lipid changes: In all instances in both treatment groups, the lipid levels increased between the baseline and 6-month visits and there were no further increases between the 6- and 12-month visits (Table I). The mean 6-month levels of total cholesterol and LDL for the propranolol and placebo groups were essentially identical, whereas the propranolol group had about a 17% higher mean level of serum triglyceride at the follow-up visits compared to the placebo group (240.4 vs 204.2 mg/dl at the 6-month visit) and about a 6% lower mean level of HDL (41.8 vs 44.4 mg/dl at the 6-month visit).

Predictive value of lipids obtained six months after infarction: The association of the 6-month lipid levels with subsequent coronary disease and mortality is shown in Table II. This analysis only includes placebo group patients and events occurring after the 6-month visit. The event rates in patients with lipid values below the median were compared with the rates in patients with values above the median. These data did not show any large association between lipid levels and coronary events. For total serum cholesterol and serum triglyceride, the trends were in the expected direction, while the opposite was noted for HDL. For all-cause mortality, all trends were in the unexpected direction. Univariate Cox regression analyses (not shown) with lipid levels as continuous variables indicated patterns similar to those in Table II.

Estimated effect of lipid changes on prognosis: The simultaneous effects of the 6-month lipid levels and treatment group assignment on coronary disease (i.e., the first occurrence of either a fatal or nonfatal coro-

TABLE II Coronary Disease and Mortality Rates from Six Months After Randomization to End of Trial by Lipid Values at Six Months in Placebo Group Only

Serum Lipid (mg/dl)	Total No. in Group	Fatal Coronary Disease (>6 months)			Fatal/Nonfatal Coronary Incidence (>6 months)			All-Cause Mortality (>6 months)		
		Rate/100	Relative Risk	Z of Diff	Rate/100	Relative Risk	Z of Diff	Rate/100	Relative Risk	Z of Diff
Total cholesterol										
≥254	791	5.1	1.12	0.49	7.7	1.11	0.60	5.4	0.86	-0.73
<254	794	4.5			6.9			6.3		
Triglyceride										
≥178	688	5.1	1.11	0.48	7.7	1.08	0.44	5.5	0.90	-0.51
<178	898	4.6			7.1			6.1		
HDL										
≥41	929	4.8	1.05	0.22	7.5	1.04	0.24	6.0	1.09	0.42
<41	651	4.6			7.2			5.5		
Estimated LDL										
≥170	737	5.0	1.00	-0.01	7.6	1.00	-0.02	5.6	0.79	-1.12
<170	656	5.0			7.6			7.0		

One to 34 months of follow-up (mean 19.4).
Lipid values are median at 6 months for both treatment groups.
Abbreviations as in Table I.

nary event, 6 months after MI) were examined using Cox models. In these bivariate analyses, lower levels of total cholesterol, triglyceride and HDL were associated with higher event rates, as were higher levels of LDL. These associations were generally weak. For example, every 1 mg/dl lower HDL value was associated with only a 1.0% increase in the coronary event rate. The preventive effect of propranolol was still highly beneficial even after adjusting for the effects of lipids. For example, there was still a 21.3% reduction in the event rate associated with propranolol use in the model that includes HDL (compared to an unadjusted 20.2% reduction) and a 16.9% reduction in the rate in the model that includes serum triglyceride.

Additional Cox regressions demonstrated the simultaneous effect of lipid change (from baseline to 6 months after MI) and treatment group assignment on coronary disease. In these bivariate analyses, reductions in the levels of serum triglyceride and HDL, and increases in the levels of total cholesterol and LDL, were associated with slightly higher event rates. Propranolol group assignment was always associated with lower event rates, however.

Other Cox regression analyses were conducted. They included: trivariate models that included baseline lipid values, lipid change values (from baseline to 6 months) and treatment group assignment as covariates; multivariate models that included lipid/treatment group interaction terms; and multivariate models that included all of the above plus characteristics known to be associated with coronary events. The results of these additional models did not differ from those already described. There was also no observed statistical interaction in the prediction of fatal/nonfatal coronary events between treatment group assignment and lipid level or change in lipid level.

In the next set of analyses, the relation between any of the lipids and all-cause mortality was inconsistent and very weak. For example, for every 1-mg-lower HDL value there was only a 0.7% relative increase in

the fatality rate. Since HDL was reduced in the propranolol group by an average of 2.6 mg/dl at the 6-month visit, it is estimated that the theoretical total increase on all-cause mortality associated with HDL reduction is approximately 2%. However, the relation between propranolol use and mortality was consistent and strong, with the propranolol-associated beneficial reduction in the fatality rate ranging from 16 to 23%. Thus, the observed benefit of propranolol is about 10 times greater than the hazard associated with HDL reduction.

As with fatal/nonfatal coronary events, other multivariate Cox regression analyses were conducted with all-cause mortality as the endpoint. Again, the results of these additional models did not differ from those described above. Furthermore, there was no observed statistical interaction between treatment group assignment and lipid level or change in lipid level.

Given these results, questions may be raised concerning the possible confounding effects of noncompliance to study medication or to use of concomitant medication. Review of the compliance data from the trial shows that about 90% of the propranolol group patients were taking a β blocker at the 3-, 6- and 12-month follow-up visits, as were less than 12% of the placebo group patients (8, 9 and 12%, respectively). With respect to other medications known to influence lipid levels (and for which the investigators collected data), there was never any strong use of or any treatment group difference for hormonal medications, insulin or any lipid-lowering agent (Table III). There was a slight increase over time in the prevalence of diuretic use in the placebo group. However, this might have the effect of raising the serum cholesterol level in this group and was not noted in Table I.

DISCUSSION

This is the largest data set to examine the issue of lipid-altering effects of β blockers after MI. However, 2 limitations with using the data set are that there are still

TABLE III Concomitant Medication Use by Treatment Group and Follow-Up Visit

Medication	at 3 Months			at 6 Months			at 12 Months		
	Prop (n = 1,749)	Placebo (n = 1,737)	Z	Prop (n = 1,701)	Placebo (n = 1,695)	Z	Prop (n = 1,686)	Placebo (n = 1,653)	Z
Diuretics (%)	21.3	23.8	-1.81	24.3	26.4	-1.40	26.3	29.4	-2.02
Hormonal medications (%)	2.0	1.6	0.86	1.9	1.5	0.92	2.3	1.9	0.77
Insulin (%)	2.9	2.8	0.17	2.9	2.8	0.09	3.0	3.0	-0.10
Lipid-lowering agents (%)	0.8	1.1	-0.89	0.7	1.1	-1.11	1.1	1.2	-0.23

Prop = propranolol group.

only about 90 deaths beyond the 6-month visit and the average length of follow-up time is short for this period (<20 months). It was necessary to select this follow-up visit as a reference point because it was the first visit at which a follow-up lipid profile was performed.

The results noted for the placebo group in Table I support data in previous reports: lipid levels tend to be lower during the first few weeks after an MI.²⁰⁻²² If it is assumed that the 6-month values reflect the ordinary (or preinfarct) values for these patients, it may be inferred that during the 3 weeks after the MI there was about a 10% reduction in serum triglyceride (≈ 20 mg/dl), 15% reductions in total cholesterol and LDL (≈ 35 and 25 mg/dl) and a 20% reduction in HDL (≈ 10 mg/dl).

The first question posed for this present analysis was: to what extent does propranolol alter lipid levels 6 and 12 months after an MI and the initiation of therapy? The effects of β blockers on lipids in general and propranolol in particular have been known for a long time from studies in hypertensive and angina patients.^{5-7,23-26} The Beta-Blocker Heart Attack Trial was the first to report these effects in a post-MI population.¹² In these previous reports, propranolol was shown to raise triglyceride levels and lower HDL within 6 months of the initiation of therapy. Although it is well accepted that a lower level of HDL is associated with increased risk of atherosclerosis, the effect of propranolol on HDL is weak. In this present analysis, the difference between the 6-month treatment group mean HDL levels is only -2.6 mg/dl, or a 6% reduction in the propranolol group (Table I). It may be noted that the propranolol-induced lower mean HDL level at 6 months (41.8 mg/dl) is still 18% higher than the mean HDL level recorded within 21 days of the infarction (35.5 mg/dl).

The effect of propranolol is stronger on serum triglyceride: the difference between the 6-month treatment group mean triglycerides is +36.2 mg/dl, or about a 17% increase in the propranolol group (Table I). Triglyceride, however, does not have a well-defined direct role in atherogenesis.²⁷

It should be emphasized that propranolol has never been reported to have an effect on the most atherogenic lipoprotein fraction, LDL. As indicated in Table I, there are essentially no propranolol-placebo group differences in the means of LDL at 6 and 12 months after MI.

The second question posed in this present analysis was: regardless of any propranolol-induced change in lipid levels, how predictive of subsequent coronary events and mortality are lipids obtained 6 months after an MI? After the lipid levels return to their ordinary levels, the data suggest that in at least the first 1.5 years after the 6-month visit, elevated lipid levels in the placebo group are not predictive of coronary events or mortality (Table II).

Other post-MI studies have also indicated that the effect of lipids on subsequent survival is weak. For example, the Coronary Drug Project, another clinical trial of post-MI patients (median length of time since last MI 22 months), has presented data in which the 15-year mortality rate for placebo group patients with a serum cholesterol ≥ 250 mg/dl was only 7% higher than the rate for placebo group patients with a cholesterol <250 mg/dl (60.2 vs 56.2%).²⁸

The third question posed in this present analysis was: is there any evidence that altered lipid levels attenuate any of the beneficial effects of propranolol on coronary morbidity and mortality? The results of the multivariate Cox regressions do not provide any evidence that the lipid-altering effects of propranolol more than marginally reduce the beneficial effects of the drug. After adjusting for lipid level, change in lipid level and treatment group/lipid level interaction, the propranolol-induced reductions in mortality and new coronary events remain on the order of 20% during the period of study. Thus the observed benefit of treatment is 10 times greater than the hazard if the lipid-related effect of propranolol on HDL in a post-MI population were to increase the risk of death by 2%.

The mechanistic bases for the improved post-MI survival associated with propranolol use include anti-dysrhythmic and antiischemic effects.⁴ The effect of propranolol on lipid levels may be unrelated to progression of atherosclerosis, for there is evidence from studies in rabbits that propranolol may actually have an antiatherogenic effect.^{29,30} This effect appears unrelated to its antihypertensive or β -blocking effects.

Finally, and regardless of any postulated adverse effect of propranolol on lipid levels, it should be recalled that the mechanisms influencing morbidity and mortality in a post-MI population are different than those in subjects free of coronary disease. The size of the infarct, the remaining function of the myocardium and any

electrical instability are more predictive of prognosis than the traditional risk factors for a first coronary event, including adverse lipid levels.⁴

These data indicate that propranolol remains an effective prophylactic treatment for patients after MI despite its metabolic effect on serum triglycerides and HDL cholesterol.

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Mechanism of Acute Myocardial Infarction in Patients with Prior Coronary Artery Bypass Grafting and Therapeutic Implications

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Although acute myocardial infarction (AMI) is usually due to thrombotic occlusion when involving a native coronary artery, the mechanism responsible for AMI in patients with previous coronary artery bypass grafting (CABG) is not well understood. Since knowledge of pathophysiology of AMI may alter subsequent management, angiograms obtained between 1 hour and 7 days of AMI (median 1 day) were reviewed in 50 patients >1 year after CABG. The culprit vessel was identified by the presence of residual stenosis and/or thrombus in the vessel supplying the infarct zone or by reviewing previous angiograms. The infarct vessel was identified as a vein graft in 38 (76%) patients, the native vessel in 8 patients (16%) and could not be accurately determined in 4 patients (8%). Among the 38 vein grafts suspected as the infarct vessel, unequivocal angiographic evidence of residual thrombus (filling defect/persistent staining) was present in 31 (82%) and was >2 cm in length in 15 patients. Successful reperfusion occurred in only 2 of 8 (25%) grafts after intravenous thrombolytic therapy. Intra-arterial thrombolysis with or without additional angioplasty was successful at restoring flow in 8 of 10 (80%) grafts. Data indicate that in patients who have undergone previous CABG, AMI is usually caused by thrombotic occlusion of a saphenous vein graft and that conventional intravenous thrombolytic therapy may be inadequate to restore flow. The large mass of thrombus and absent flow in the graft may require subselective drug infusion, a higher thrombolytic dose or a mechanical means of recanalization.

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When acute myocardial infarction (AMI) involves a native coronary artery, it is usually due to a plaque rupture and thrombus.¹ Although early occlusion of a saphenous vein graft is almost always due to acute thrombus, late graft occlusion has often been attributed to fibrosis or atheromatous occlusion.²⁻⁷ Previous case reports have shown that intra-arterial thrombolytic therapy may open bypass grafts that occlude in the first several weeks after the operation.⁸⁻¹⁴ Despite the increasing number of patients with prior coronary artery bypass grafting (CABG) who present with AMI, few data exist regarding the appropriate reperfusion strategy. Patients with previous CABG have usually been excluded from reperfusion trials using acute angiography. Therefore, it is not known how frequently AMI in such patients involves a bypass graft as opposed to the native coronary vessel distal to graft insertion or occlusion of a nonbypassed native artery. Furthermore, the efficacy of reperfusion therapy in this population has not been established. Thus, we reviewed the records of patients who presented with AMI >1 year after CABG to determine the following: the frequency of bypass graft involvement resulting in AMI; the mechanism responsible for the AMI; and the efficacy of reperfusion therapy in this population.

METHODS

Medical records of patients with prior CABG who underwent cardiac catheterization (n = 46) or autopsy (n = 4) within 1 week of AMI from 1981 to 1988 were retrospectively reviewed. AMI was confirmed by a transient increase of creatine kinase and its MB fraction in association with ischemic chest pain of ≥ 30 minutes duration and electrocardiographic changes consisting of new Q waves, ST-segment elevation or depression, or T-wave inversions. Patients who had undergone CABG within 1 year of AMI were excluded since the mechanism of AMI in the early postoperative period may differ from that of late AMI.

All 46 cineangiograms were reviewed by a single observer. The presence of thrombus was defined as a circular or mottled intraluminal filling defect or persistent contrast staining. The length of thrombus was determined by calipers using the known dimension of the angiographic catheter as a reference. The infarct vessel was identified based on electrocardiographic changes and wall motion abnormalities on biplane ventriculography that occurred in the distribution of a vessel containing a high-grade residual stenosis (n = 4) and/or

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thrombus (n = 32) or total occlusion in the mid- or distal graft without obvious thrombus (n = 2). When available, previous angiograms (n = 14) were compared to postinfarction angiograms and allowed identification of infarct-related vessel in 4 additional patients. The culprit vessel could not be determined in 4 patients. Infarct vessel patency was determined according to the Thrombolysis in Myocardial Infarction study classification.¹⁵

RESULTS

Patient characteristics: Of the 50 patients who met inclusion criteria for the study, 47 (94%) were men and the mean age was 58 ± 8 years. Cardiac risk factors at the time of AMI included cigarette smoking (83%), systemic hypertension (66%) and diabetes mellitus (17%). A history of previous AMI was present in 25 (50%) and angina within the prior week was present in 23 (46%) patients. The mean interval from CABG to AMI was 6.6 ± 3.3 years (range 1 to 15). The current infarction resulted in new Q waves in 33 (66%) patients and all patients had elevation of creatine kinase with a mean peak level of $2,144 \pm 1,768$ U/liter (range 231 to 9,170). Eleven patients were initially treated with intravenous thrombolytic therapy consisting of either 1.5 million U of streptokinase (n = 8) or 100-mg tissue plasminogen activator (n = 3) within 6 hours of symptom onset.

Angiographic and pathologic findings: Four patients died during hospitalization for AMI and the culprit vessel was determined by autopsy. The remaining 46 patients underwent cardiac catheterization within 1 week of infarction (mean 1.6 ± 2.3 days; median 1 day). As listed in Table I, the infarct-related vessel was the native coronary artery in 8 patients (16%). Native vessel occlusion occurred in 3 arteries that were not grafted, 3 arteries in which the corresponding vein graft was chronically occluded and 2 arteries in which the corresponding graft was patent but the native vessel occluded proximal (n = 1) or distal (n = 1) to the graft anastomosis. The culprit vessel was the saphenous vein graft in 38 patients (76%) and could not be determined in 4 patients (8%). Unequivocal evidence of thrombus was present in 5 of 8 (63%) native infarct arteries and in 31 of 38 (82%) vein grafts (Figure 1). In 15 of the vein grafts, the thrombus was very extensive (>2 cm in length) and filled the entire length of the graft in many patients.

Of the 11 patients who received intravenous thrombolytic therapy, infarct vessel patency was achieved in 3 of 3 (100%) native coronary arteries, but in only 2 of 8 (25%) were saphenous vein grafts determined to be the culprit vessel (Figure 2). A salvage angioplasty procedure or subselective infusion of a thrombolytic drug was attempted in 4 grafts that remained occluded after intravenous thrombolytic therapy and was successful at restoring flow in all cases (Figure 3). A more direct approach of emergency catheterization with intragraft thrombolytic therapy with or without additional balloon angioplasty was successful at restoring patency in 8 of 10 (80%) occluded saphenous vein grafts (Figure 4).

TABLE I Angiographic/Pathologic Findings

Date of study from AMI (days)	1.6 ± 2.3 (median 1)
Infarct vessel	
Native artery	8 (16%)
Vein graft	38 (76%)
Not determined	4 (8%)
Thrombus in infarct vessel	
Native artery	5 (63%)
Vein graft	31 (82%)
	(>2 cm in 14)

AMI = acute myocardial infarction.

Intragraft streptokinase (150,000 to 250,000 U) was used in 5 patients and urokinase (500,000 U) in the remaining 5 patients. Direct coronary angioplasty was successful at restoring flow in 2 of 2 (100%) native coronary arteries. In 1 patient who underwent catheterization within 1 hour of chest pain onset, successful reperfusion of the saphenous vein graft was achieved with contrast injections only and the patient underwent emergency bypass grafting.

Although intragraft thrombolytic therapy was highly successful at restoring flow, a residual thrombus was usually present and was managed with aspirin and heparin therapy until the time of discharge. Distal embolization of thrombotic material was not angiographically apparent after thrombolytic therapy or angioplasty. However, angioplasty was usually avoided in grafts containing abundant thrombus.

Clinical outcome based on infarct vessel patency: Excluding 8 patients, 4 in whom data were obtained by autopsy alone and 4 in whom the infarct vessel could not be identified, in-hospital clinical outcome based on infarct vessel patency is listed in Table II. At catheterization, a patent infarct vessel occurred either spontaneously or after reperfusion therapy in 19 patients. Two patients experienced recurrent chest pain and reocclusion was angiographically documented with repeat angiography. One patient (5%) with previous inferior and

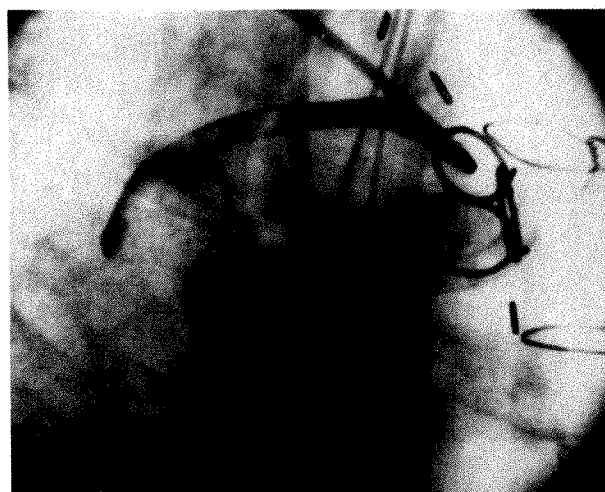


FIGURE 1. This 64-year-old man presented with a non-Q-wave myocardial infarction. Angiography performed 1-day after infarction showed a large thrombus in left anterior-descending graft with no anterograde flow. Patient was managed with medical therapy.

TABLE II Clinical Outcomes Based on Infarct Vessel Patency*

	Patent (%) (n = 19)	Occluded (%) (n = 23)
Reocclusion	2 (11)	NA
Elective CABG/PTCA	5 (26)	7 (30)
Medical therapy	11 (58)	11 (48)
Death	1 (5)	5 (22)

* 8 patients excluded (unable to identify infarct vessel in 4); data obtained by autopsy alone in 4.
CABG = coronary artery bypass grafting; NA = not available; PTCA = percutaneous transluminal coronary angioplasty.

new anterior infarctions died of cardiogenic shock despite streptokinase-mediated reperfusion of the graft. The remaining 16 patients remained stable and were managed with medical therapy (n = 11) and/or subsequent elective revascularization with bypass grafting or angioplasty (n = 5).

The infarct vessel remained occluded at the termination of catheterization in 23 patients. Five of these patients (22%) died of cardiogenic shock despite aggres-

sive inotropic support as well as intraaortic balloon counterpulsation. Bypass grafting or angioplasty was subsequently performed electively in 7 patients and the remaining 11 patients were managed medically.

DISCUSSION

Although thrombosis is the mechanism for early graft occlusion, fibrosis or atherosclerosis was thought to be responsible for late vein graft occlusion.²⁻⁷ Thrombus superimposed on a ruptured plaque was not regarded as a significant cause of late graft occlusion until Walts et al¹⁶ described this finding in saphenous vein grafts of 10 patients who underwent autopsy after AMI. In this series, an additional 52 of 119 (44%) patients in whom vein grafts were excised at the time of elective reoperation showed recent thrombus. Walts concluded that thrombus on a ruptured atheroma was a common mechanism of late graft occlusion and may be amenable to thrombolytic therapy. However, most trials of thrombolytic therapy have excluded patients with prior CABG, primarily due to the perceived difficulty in identifying the infarct-related vessel. Thus, little pub-

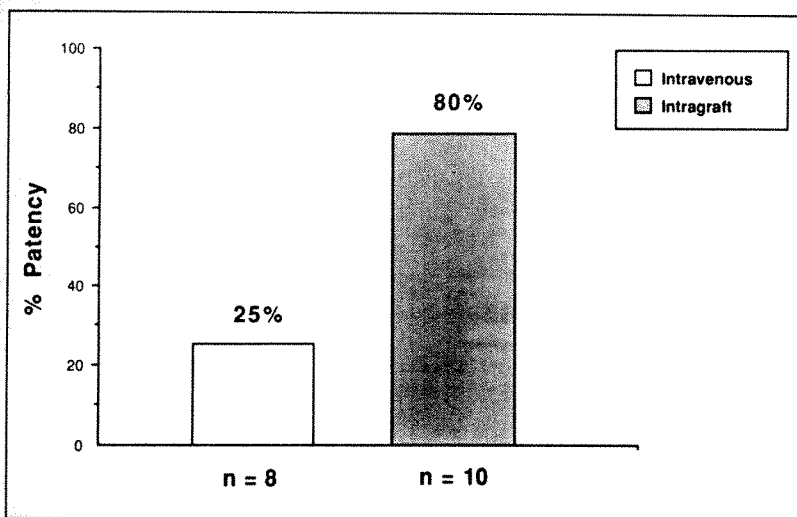


FIGURE 2. Differences in patency of infarct-related graft after intravenous thrombolytic therapy (25%) and intragraft thrombolytic therapy (80%). $P = 0.02$.

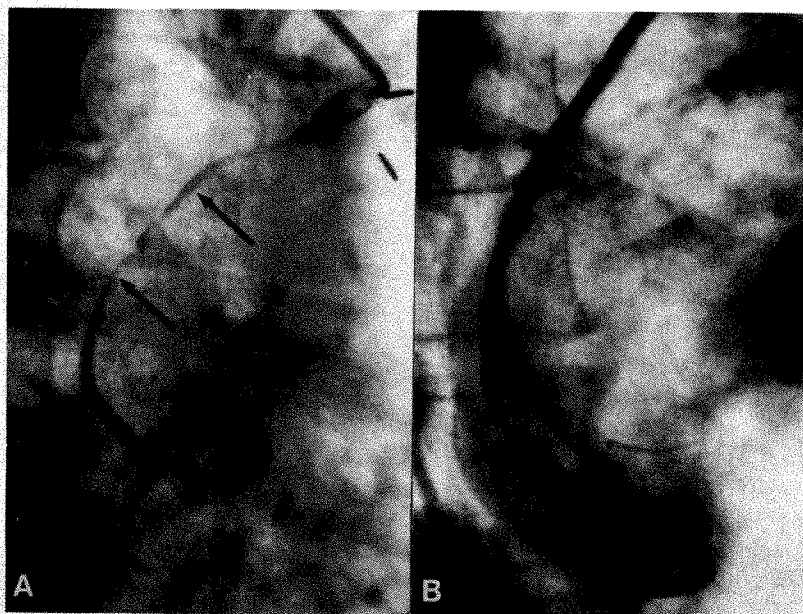


FIGURE 3. Fifty-four-year-old man who presented with acute inferior myocardial infarction and received 1.5 million U intravenous streptokinase. **A**, emergency angiography showed extensive thrombus within circumflex graft with total occlusion in distal graft. **B**, an additional 250,000 U intragraft streptokinase resulted in reperfusion.

lished information is available regarding thrombolysis in this population except for isolated case reports.¹⁷⁻¹⁹

Our retrospective review shows that in patients with a remote history of CABG, AMI is usually due to thrombotic occlusion of a saphenous vein graft and is infrequently due to acute occlusion of the native vessel. Lesions in the native vessel proximal to the graft anastomotic site are known to have accelerated atherosclerosis.²⁻⁶ This process may result in total occlusion of the proximal native coronary artery within the first few postoperative years. Since the majority of grafts remain patent at this time, occlusion of the native vessel may not result in infarction. Over the next several years, however, atherosclerosis of the graft or distal native vessel may occur. Plaque rupture or slow flow in the graft due to poor runoff may then result in thrombotic graft occlusion and subsequent infarction.

In our experience, intravenous thrombolytic drugs were successful at restoring flow in only 2 of 8 grafts (25%). Conversely, intragraft thrombolytic therapy with or without additional angioplasty resulted in reperfusion in 8 of 10 grafts (80%). Absence of side branches or distal runoff may result in a stagnant column of blood with rapid propagation of thrombus within the graft. Absence of flow within the graft may also prevent delivery of an intravenously administered drug to the site of the thrombus. Both the large mass of thrombus and absent flow in the graft may account for the low patency rate after intravenous thrombolytic therapy in this study. Our observation differs from that of Kleiman et al,²⁰ who reported 5 patients with AMI 5 to 8 years after CABG who were treated with intravenous tissue plasminogen activator. Clinical signs of reperfusion were present in 4 patients (80%). Although the status of the native vessel was not reported, catheterization performed before hospital discharge revealed a patent graft in the distribution of the infarct in all 5 patients. The greater patency rate observed by Kleiman may relate to the use of tissue plasminogen activator, which has been reported to be a more potent thrombolytic agent compared with streptokinase.¹⁵ Conversely, with catheterization performed relatively late during the hospital course, precise identification may have been difficult and spontaneous thrombolysis of the infarct vessel may have occurred.²¹

Reocclusion occurred in 2 of 19 patients with a patent infarct vessel at initial catheterization. Since follow-up catheterizations were not routinely performed, the actual incidence of reocclusion may be far >10%. With underlying mechanical problems including critical graft stenoses, anastomotic lesions, poor distal runoff due to a small native vessel or large residual thrombi, vein grafts may be at increased risk for reocclusion. Although the numbers are small, mortality tended to be greater in patients with an occluded infarct-related vessel. Restoration of flow in the graft may have resulted in salvage of myocardium and improved survival. However, due to the retrospective nature of this study, the beneficial effects of reperfusion therapy could not be precisely determined.

Limitations: This study was derived from a retrospective review of a small group of patients; thus, it

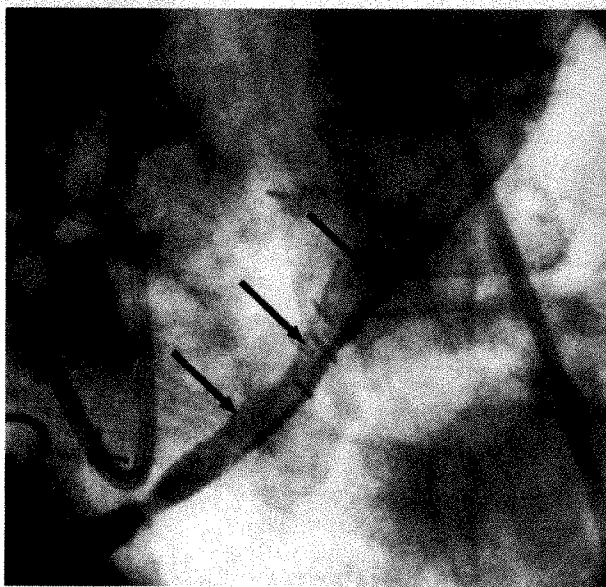


FIGURE 4. Sixty-nine-year-old man 5 years after bypass with acute lateral myocardial infarction. Emergency angiography revealed occlusive thrombus filling entire circumflex graft. Intragraft urokinase was successful at restoring flow.

must be interpreted with caution. Since the study criteria required either autopsy or cardiac catheterization to have been performed, selection bias for the sickest patients is likely. Furthermore, no uniform approach to reperfusion therapy was used. Thus, the efficacy of various thrombolytic drugs and routes of administration in the population remains uncertain and will require a prospectively conducted trial.

Clinical implications: In patients who have undergone previous CABG, AMI is usually due to acute thrombotic occlusion of a saphenous vein graft. Although an intravenous thrombolytic agent should probably be administered, conventional approaches may be inadequate to restore flow. Due to the abundance of clot and the absence of antegrade flow preventing delivery of drug to the thrombus, additional intragraft thrombolytic therapy may be necessary. An alternative approach is to perform angioplasty of the native vessel proximal to the graft insertion site, or of the graft itself. Although reperfusion therapy in patients with bypass grafts holds promise, data regarding acute patency rates and long-term clinical and angiographic follow-up are lacking. Thus, the precise role of intravenous or intragraft thrombolytic therapy or angioplasty in this patient population will require further study.

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Hemodynamic and Oxygen Transport Variables in Cardiogenic Shock Secondary to Acute Myocardial Infarction, and Response to Treatment

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There are few data on oxygen transport in cardiogenic shock after acute myocardial infarction. This prospective study examined oxygen transport variables in 19 such patients and assessed their responses to treatment. Femoral and pulmonary arterial catheters were inserted before any therapy except correction of hypoxemia by mechanical ventilation in 8 patients, defibrillation (3 patients) or pacing (5 patients). In 3 patients mean arterial pressure was >80 mm Hg and cardiac index >2.1 liters/min/m² with normal mixed venous oxygen saturation despite simultaneous clinical shock. They recovered with no further treatment. Sixteen patients were treated with varying combinations of intravenous fluids and dobutamine (37 ± 25 μ g/kg/min) and 14 survived long enough for a second set of measurements to be completed. Mean heart rate increased from 83 ± 22 to 101 ± 20 beats/min and mean cardiac index from 1.4 ± 0.5 to 2.5 ± 0.4 liters/min/m² ($p < 0.001$). Oxygen consumption (VO_2) was maintained even when oxygen delivery (DO_2) was <330 ml/min/m². After treatment DO_2 increased from 230 ± 69 to 397 ± 60 ml/min/m² ($p < 0.001$) and VO_2 from 103 ± 31 to 124 ± 27 ml/min/m² ($p < 0.05$). Mean mixed venous oxygen saturation increased from 54 ± 16 to $69 \pm 8\%$ ($p < 0.001$) and mean oxygen extraction ratio decreased from 48 ± 16 to $31 \pm 6\%$ ($p < 0.001$). There was no correlation between cuff systolic blood pressure and mean arterial pressure before or after resuscitation. Thirteen patients survived to hospital discharge. When cardiogenic shock responds to treatment, large increases in DO_2 lead to small increases in VO_2 but large increases in mixed venous oxygen saturation, reflecting improved tissue oxygen availability.

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Cardiogenic shock after acute myocardial infarction has an extremely poor, if not hopeless, prognosis.^{1,2} The outlook may be better for those patients without a critically elevated pulmonary artery occlusion pressure.³⁻⁵

Oxygen transport patterns and responses to treatment have been well defined in hemorrhagic, traumatic and septic shock^{6,7} and levels of cardiac index, oxygen delivery (DO_2) and oxygen consumption (VO_2) have been identified as being associated with improved survival rates.^{8,9} This is not the case in cardiogenic shock. Critically low levels of mixed venous oxygen saturation have been described in individual cases of cardiogenic shock in mixed series of patients.¹⁰⁻¹³ The low levels of cardiac index reported in most series suggest that DO_2 may be reduced to levels below those thought to be critical in humans.¹⁴ However, there are no data on the response of oxygen transport variables to successful treatment.

We prospectively studied the oxygen transport patterns in 19 such patients with shock and wherever possible the responses to resuscitation.

METHODS

We studied 19 consecutive patients referred for further treatment of cardiogenic shock. Their clinical, electrocardiographic and biochemical data are listed in Table I. All patients had a cuff systolic blood pressure <70 mm Hg, abnormal conscious level (drowsiness or coma) and anuria. The mean age was 60 years (range 46 to 74) and 12 were men. The electrocardiographic site of infarction was inferior in 15, anterior in 2 and posterior in 2, with lateral extension in 4. Nine patients had had a previous myocardial infarction and 1 had undergone coronary artery bypass surgery.

Femoral and pulmonary artery catheters were inserted before any therapy except the correction of hypoxemia, which required tracheal intubation and mechanical ventilation in 8 patients, defibrillation (3 patients) and insertion of temporary transvenous pacing electrodes for complete heart block (5 patients). Measurements of mean systemic arterial blood pressure, cardiac output, right atrial pressure, pulmonary artery pressure and pulmonary artery occlusion pressure were made (7000 series bedside monitors, Marquette Electronics). From these measured variables cardiac index, stroke volume index, left ventricular stroke work index and systemic vascular resistance index were calculated

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TABLE I Patient Data

Pt	Age (yrs), Sex	Site of Infarct	Previous CAD	Maximum		Other Diseases	IPPV	Defib	Paced	Outcome
				CK	AST					
1	48, M	Inferior		4,962	500	0	+	0	0	S
2	46, M	Inferior	MI, CABG	3,144	295	0	+	0	0	S
3	60, F	Inferior		2,400	—	SH	0	0	+	S
4	65, F	Inferior		1,850	244	0	+	+	0	S
5	51, F	Inferior		1,670	717	DM	+	0	0	S
6	69, M	Inferior		2,100	315	PVD	0	0	0	S
7	67, F	Anterior	MI	2,320	142	0	0	0	+	S
8	76, M	Inferior	MI	1,500	—	SH	0	0	0	S
9	49, M	Inferior		1,721	—	0	0	0	0	S
10	69, F	Inferior		874	232	Arthritis	0	0	0	S
11	58, M	Inferior	Angina, LBBB	3,955	—	COPD, PVD	+	0	+	NS
12	73, M	Anterior	MI	2,420	—	SH	+	+	0	NS
13	56, M	Inferior	MI	340	182	SH	+	0	0	NS
14	53, M	Inferior	MI	2,215	420	SH, DM	0	0	0	NS
15	63, F	Inferior	MI	—	—	SH	0	0	+	NS
16	74, M	Inferior	MI x 2	—	—	0	0	+	+	NS
17*	47, M	Inferior		347	—	0	0	0	0	S
18	56, F	Inferior	MI	605	—	SH	0	0	0	S
19	50, M	Inferior		1,336	167	0	+	0	0	S

* Survived shock but died later from ventricular rupture.

AST = aspartate transaminase (IU/liter); CABG = coronary artery bypass graft; CAD = coronary artery disease; CK = creatine kinase (IU/liter); COPD = chronic obstructive pulmonary disease; Defib = patients defibrillated; DM = diabetes mellitus; IPPV = intermittent positive pressure ventilation; LBBB = left bundle branch block; MI = myocardial infarction; NS = nonsurvivor; PVD = peripheral vascular disease; S = survivor; SH = systemic hypertension; + = present; 0 = absent; — = not measured.

TABLE II Hemodynamic and Oxygen Transport Variables of the Patients

	HR	MAP	CI	SVI	LVSWI	PAOP	SVRI	DO ₂	VO ₂	SvO ₂	OER
Group A (n = 2)	92 ± 11	59 ± 20	0.9 ± 0.4	10 ± 4	6 ± 1	22 ± 17	2,369 ± 2,615	161 ± 44	105 ± 57	39 ± 18	63 ± 19
Group B (n = 3)	85 ± 28	73 ± 14	2.3 ± 0.2	29 ± 10	21 ± 7	22 ± 7	1,050 ± 280	351 ± 61	105 ± 7	71 ± 7	30 ± 6
Group C (n = 14)											
Before therapy	83 ± 22	66 ± 14	1.3 ± 0.5	17 ± 6	12 ± 6	15 ± 7	1,904 ± 897	230 ± 69	103 ± 31	54 ± 16	48 ± 16
After therapy	101 ± 20	81 ± 9	2.5 ± 0.4	25 ± 6	22 ± 7	18 ± 3	1,131 ± 254	397 ± 60	124 ± 22	69 ± 8	31 ± 6

Values are mean ± standard deviation.

CI = cardiac index; DO₂ = oxygen delivery; HR = heart rate; LVSWI = left ventricular stroke work index; MAP = mean arterial blood pressure; OER = oxygen extraction ratio; PAOP = pulmonary artery occlusion pressure; SVI = stroke volume index; SvO₂ = mixed venous oxygen saturation; SVRI = systemic vascular resistance index; VO₂ = oxygen consumption.

using standard formulas. Samples of blood were taken from the femoral and pulmonary artery catheters for measurements of oxyhemoglobin saturations using an oximeter (co-oximeter model I.L. 282). Arterial and mixed venous oxygen contents, DO₂, VO₂ and oxygen extraction ratios were calculated, again from standard formulas.

The patients were managed according to a previously approved protocol. If pulmonary artery occlusion pressure was <14 mm Hg, then controlled plasma volume expansion with colloid was undertaken as previously described.^{3,15} This failed to increase the clinical, hemodynamic or oxygen transport status significantly. Therefore, dobutamine infusion was started at 5 µg/kg/min, with increases guided by frequent measurements of pulmonary artery occlusion pressure and cardiac output. Infusion was continued until maximal increases in stroke volume index had been obtained without an unacceptable tachycardia (heart rate 130 beats/min), significant dysrhythmia or worsening of ST-segment changes, as measured automatically from 5 leads. The intubated patients were ventilated at a rate of 10

breaths/min and tidal volume 12 ml/kg using volume-cycled ventilators.

During the study period no procedures were undertaken or treatments given that might affect oxygen transport. When maximal improvement in stroke volume index had been obtained, the hemodynamic and oxygen transport measurements were repeated. None of the study patients had received thrombolytic therapy.

Statistical analysis of the values before and after treatment was by the Wilcoxon signed rank test.

RESULTS

Table II lists the hemodynamic and oxygen transport data of the patients studied. Values are mean ± standard deviation before and after treatment. In 5 patients only the initial measurements are available; 2 of these died before the measurements could be repeated (group A). The other 3 patients had relatively normal hemodynamic and oxygen transport variables despite simultaneous clinical findings of cardiogenic shock (group B). One patient in group B (patient 9) required intubation and mechanical ventilation for episodic ap-

nea. His arterial carbon dioxide tension was 8.2 kPa (62 mm Hg) immediately before intubation. Apart from this no therapeutic interventions were made in group B patients. All 3 recovered from the shock episode but 1 died 6 days later from rupture of the free wall of the left ventricle (patient 17). The other 2 were hospital survivors. In 14 patients a second set of measurements was obtained (group C). In summary, there were highly significant increases in mean arterial pressure (66 ± 14 to 81 ± 9), cardiac index (1.4 ± 0.5 to 2.5 ± 0.4 liters/min/m²), stroke volume index (17 ± 6 to 25 ± 6 ml/m²), left ventricular stroke work index (12 ± 6 to 22 ± 7 g · m/m²), DO₂ (230 ± 69 to 397 ± 60 ml/min/m²) and mixed venous saturation (54 ± 16 to $69 \pm 8\%$), with small but significant increases in heart rate (83 ± 22 to 101 ± 20 beats/min) and VO₂ (103 ± 31 to 124 ± 22 ml/min/m²), and significant decreases in systemic vascular resistance index ($1,904 \pm 897$ to $1,131 \pm 254$ dynes · s · cm⁻⁵ · m⁻²) and oxygen extraction ratio (48 ± 16 to $31 \pm 6\%$). End-expiratory pulmonary artery occlusion pressure increased from 15 ± 7 to 18 ± 3 mm Hg. The improvement in left ventricular stroke work index in relation to the pulmonary artery occlusion pressure is shown in Figure 1. The time between measured hemodynamic improvement and observed improvement in the patients' clinical status varied. The most objective clinical sign of improvement was reversal of anuria. This occurred 0.5 to 2.2 hours after achieving the maximum improvements in hemodynamic and oxygen transport variables. There was no correlation between the noninvasive and invasive blood pressure recordings before or after resuscitation.

The doses of dobutamine required to achieve the increase in cardiac index and DO₂ ranged from 7 to 93 µg/kg/min, with a mean of 37 µg/kg/min. No patient survived if doses of >48 µg/kg/min were necessary. Thirteen of 19 patients were hospital survivors (68%). All nonsurvivors had had a previous episode of proven myocardial infarction.

DISCUSSION

Oxygen transport patterns in subsets of patients with cardiogenic shock have been investigated in 2 previous studies.^{12,13} Both groups found, as we did, that VO₂ was reduced in the face of critically low values of DO₂. This is despite increases in oxygen extraction ratio, which lead to decreases in mixed venous saturation, often to critically low levels. These studies showed an inverse relation between VO₂ and serum lactate levels, but no attempt was made to compare the oxygen transport patterns before and after resuscitation. Many patients had been treated with adrenergic agents before measurement of oxygen transport variables. In the current study we have confirmed the low levels of DO₂, VO₂ and mixed venous saturation due to low levels of cardiac index as normal levels of arterial oxygen content were obtained by correction of hypoxemia as the first priority. The patients would undoubtedly have had a lower arterial oxygen tension before such measures and therefore the initial DO₂ levels would have been even lower. Some patients (1, 2, 6, 8, 14 and 15) had maintained VO₂ with DO₂ levels below those thought to be critical.¹⁴

The VO₂ in these patients was achieved by large increases in oxygen extraction ratio leading to mixed venous saturations approaching 40%, which may be critical.¹⁶ In 1 nonsurvivor mixed venous saturation was recorded at 26% immediately before the development of asystole.

In an early study of patients with well-established acute myocardial infarction, a close correlation between measured hemodynamics and clinical assessment of cardiac output and left ventricular preload was shown.¹⁷ The investigators did note, however, that when hemodynamics were altered by management there was poor correlation between hemodynamics and physical status. In more unstable patients a poor correlation between physical signs and documented left ventricular failure was found.¹⁸ There is a time lag between physiologic resolution of left ventricular failure and improvement on clinical and radiologic grounds.¹⁹ The findings of acceptable hemodynamics in 3 of the patients in the present study with simultaneous clinical signs of cardiogenic shock shows that a similar latent interval may be seen in cardiogenic shock. We assume that the 3 patients had been in cardiogenic shock but that hemodynamics had improved spontaneously. The proportion of such patients may be small but significant and their treatment with catecholamines is not only unnecessary but dangerous. Inclusion of such patients into a study of new treatments will give misleading results.

This was a consecutive series of patients referred by attending physicians for management. It is evident that there was preselection in that a relatively high proportion with shock after inferior myocardial infarction are included. Also, patients with disabling diseases before development of cardiogenic shock may not have been referred.

We confirmed the poor correlation between invasive and noninvasive blood pressure measurements when systemic vascular resistance is high in shock patients.²⁰ As noninvasive blood pressure measurement underestimates the true blood pressure, we recommend that no

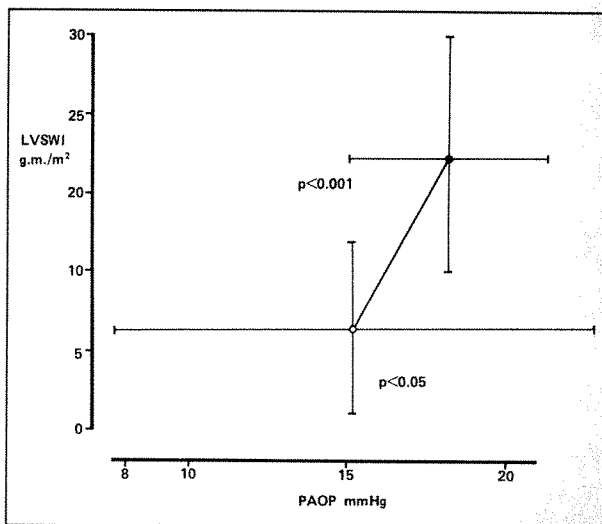


FIGURE 1. Mean changes in left ventricular stroke work index (LVSWI) and pulmonary artery occlusion pressure (PAOP) before (○) and after (●) treatment in 14 patients in whom a second set of measurements was obtained.

vasoactive drugs, especially vasopressor agents, are given without invasive blood pressure measurement, as their need may be more apparent than real. The true need may well be not for more pressure but for more flow.

In 13 patients cardiac index and DO_2 increased. The decreases in arterial oxygen tension seen in some patients were not sufficient to lower arterial oxygen content significantly. VO_2 increased but more significantly so too did the mixed venous saturation. The oxygen extraction ratio decreased as overall oxygen availability increased. In traumatic shock, survival rates have been shown to correlate with supranormal rather than normal values of cardiac index, DO_2 and VO_2 .⁹ After cardiac infarction, survival rates of 80% have been reported with cardiac index of 2.2 to 2.4 liters/min/m².¹⁷ Our results also show that in shock after acute myocardial infarction, survival can be achieved by attaining these levels of cardiac index soon after presentation. It is difficult and dangerous to try for higher levels.

We suggest that it may be relevant to measure oxygen transport variables during resuscitation from cardiogenic shock and to titrate therapy against increases in mixed venous saturation. If this approaches 60%, then oxygen availability is such that survival is possible.

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Anatomic Validation of Electrocardiographic Estimation of the Size of Acute or Healed Myocardial Infarcts

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Seventeen new criteria added to the simplified version of the Selvester QRS scoring system to comprise the complete version were evaluated to determine their value in estimating the size of single infarcts. These non-Q-wave criteria might be particularly useful regarding posterolateral infarcts in the distribution of the left circumflex artery. The study population was made up of 21 anterior, 30 inferior and 20 posterolateral single myocardial infarction (MI) patients with no evidences of bundle branch or fascicular blocks, ventricular hypertrophy or previous MI on their final stable electrocardiogram. The complete system's maximum 32 points is capable of indicating MI in 96% of the left ventricle and it estimated a mean electrocardiographic MI size that better approximated the anatomic size compared with the simplified version in all MI locations. The correlation between anatomic and electrocardiographic MI size using the complete system was better and statistically significant for the posterolateral MI group (simplified $r = 0.55$, $p < 0.01$ vs complete $r = 0.70$, $p < 0.0006$). Criteria such as Q and S amplitude ≤ 0.3 mV in V_1 and ≤ 0.4 mV in V_2 were particularly helpful. This study documents the improved ability provided by the 17 additional non-Q-wave criteria which have been added in the complete version of this scoring system regarding the sizing of infarcts in the region of the left ventricle supplied by the left circumflex artery.

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Myocardial infarct (MI) size determination is clinically important since patient prognosis,¹ left ventricular function² and frequency of ventricular arrhythmias³ correlate well with the amount of myocardium infarcted; knowledge of the size of the infarct influences the clinician's therapeutic decisions.⁴ Several methods of sizing infarcts using electrocardiographic criteria have been proposed,⁵⁻⁷ but only the Selvester system uses weighted criteria in multiple leads based on the activation sequence of the human heart.⁸

The simplified Selvester QRS scoring system introduced by Wagner et al,⁹ which consisted of 37 quantitative criteria representing abnormalities commonly used for MI diagnosis, has been validated with anatomic studies of single MIs in different regions of the left ventricle.¹⁰⁻¹² The correlation was excellent for MIs in the anterior location, but only moderate for those in the inferior and posterolateral areas. Other studies have also indicated that the existing classic electrocardiographic criteria are particularly insensitive to changes in the posterolateral region.¹³⁻¹⁵ Hindman et al¹⁶ subsequently evaluated the specificity of the 17 additional criteria which had been originally proposed by Selvester,⁸ many of which were designed to indicate posterolateral infarction. However, there has been no documentation of the sensitivity of these new criteria.

This study evaluates the 17 additional criteria contained in the complete Selvester QRS scoring system to determine their value in estimating the anatomically documented size of single acute or healed MIs in each of the 3 major coronary artery distributions of the left ventricle. It was hypothesized that there would be maximally improved correlation regarding the posterolateral myocardium which is supplied by the left circumflex artery.

METHODS

Patient population: Deceased patients from 8 collaborating medical centers¹⁰⁻¹² were included in the study if they had the following: an anatomically identifiable single acute or healed MI of the left ventricle; no evidence of cardiac rupture or surgical resection of the left ventricle; and a post-MI electrocardiogram obtained within 1 year of death that did not exhibit confounding factors, such as bundle branch or fascicular blocks, ventricular hypertrophy or previous MIs. Patients were divided into anterior, inferior and posterolateral groups according to anatomic MI location, as described below.

These constitute the same patients that were included in previous reports.¹⁰⁻¹²

Quantitative anatomic evaluation: The hearts, collected at the Duke Cardiovascular Pathology Laboratory between 1969 and 1980, were prepared and studied at the time of autopsy by previously described methods.¹⁷⁻²⁰ Of >500 patients examined, 71 met the criteria for inclusion. The left ventricle was first divided into thirds by drawing a line from the centroid to the midpoint of the septum (Figure 1A). From this reference,

the heart was divided into anterior, inferior and posterolateral thirds, corresponding approximately to the following 3 major coronary artery distributions: left anterior descending; right coronary; and left circumflex. The greatest percent MI in any third determined the location. Anatomic percent MI was quantitated by the method of Ideker et al^{10,18} which involved cutting the ventricles into 5 to 6 transverse slices of approximately equal thickness (Figure 1B), taking sections of each slice for histologic studies and calculating the amount of

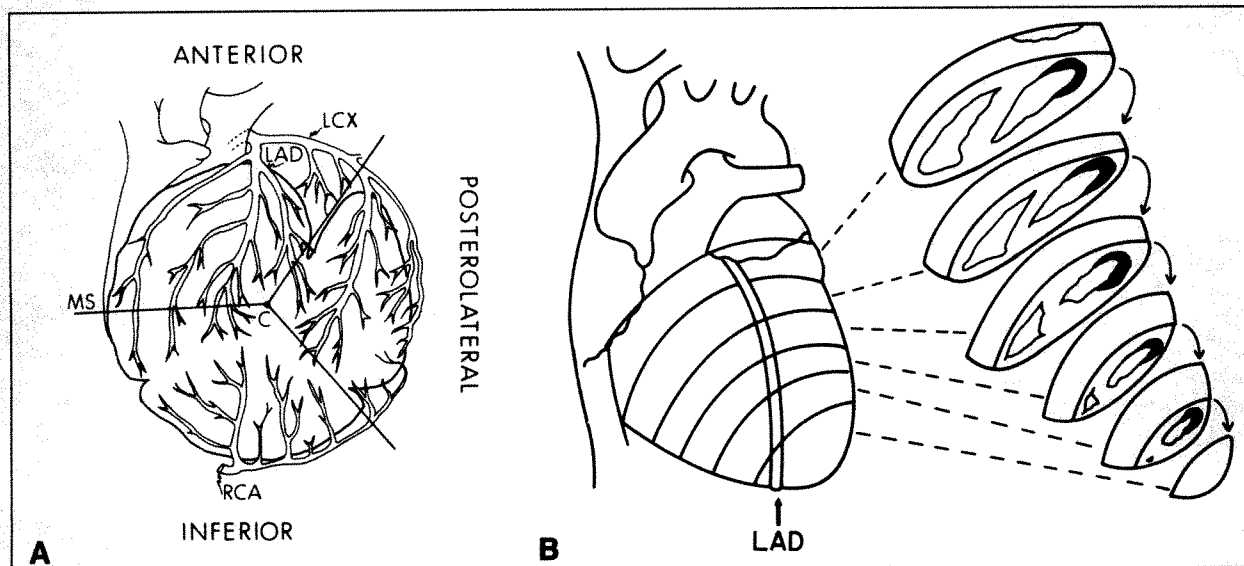


FIGURE 1. *A*, division of left ventricle into equiangular thirds corresponding to distributions of 3 major coronary vessels. Left ventricle is seen in projection viewed from apex. Right ventricle has been removed and the anterior wall or septum is to the left. *B*, top of each slice was photographed and histologic sections were taken from bottom of each slice to outline area of the infarct of contiguous slice (*arrows*). Solid areas represent infarction involving posterolateral region. *C* = centroid of epicardial outline of left ventricle and of right septal border; LAD = left anterior descending artery; LCX = left circumflex artery; MS = reference point in midseptum; RCA = right coronary artery.

Complete 54-Criteria/32-Point QRS Scoring System									
Lead	Max Lead Points	Criteria	Pts	V ₁	V ₂	V ₃	V ₄	V ₅	V ₆
I	(2)	Q ≥ 30 ms R/Q ≤ 1 R ≤ 0.2 mV*	(1) (1) (1)	(2) Any Q Q or S ≥ 1.8 mV*	(1) Any Q R ≤ 10 ms R ≤ 0.1 mV* R ≤ R V ₁ mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*
II	(2)	Q ≥ 40 ms Q ≥ 30 ms	(2) (1)	(4) R/S ≥ 1 R ≥ 50 ms R ≥ 1.0 mV* R ≥ 40 ms R ≥ 0.6 mV*	(1) Any Q R ≤ 10 ms R ≤ 0.1 mV* R ≤ R V ₁ mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*
aVL	(2)	Q ≥ 30 ms R/Q ≤ 1	(1) (1)	Q and S ≤ 0.3 mV*	(4) R/S ≥ 1.5 R ≥ 60 ms R ≥ 2.0 mV* R ≥ 50 ms R ≥ 1.5 mV*	(1) Any Q R ≤ 10 ms R ≤ 0.1 mV* R ≤ R V ₁ mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*
aVF	(5)	Q ≥ 50 ms Q ≥ 40 ms Q ≥ 30 ms R/Q ≤ 1 R/Q ≤ 2	(3) (2) (1) (2) (1)	Q and S ≤ 0.4 mV*	(1) Any Q R ≤ 10 ms R ≤ 0.1 mV* R ≤ R V ₁ mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*	(1) Any Q R ≤ 20 ms R ≤ 0.2 mV*

* New criterion. Max = maximal.

FIGURE 2. When >1 criterion in bracket is met, the one with most points is selected. "Notched R" indicates a notch that begins within first 40 ms. Reproduced from Hindman et al¹⁶ with permission of the publisher.

infarction by computer assisted planimetry. Detailed descriptions of these techniques have been presented previously.^{10-12,18-20}

Electrocardiogram analysis: The final stable electrocardiogram was identified for each patient. This electrocardiogram had no changes typical of electrolyte imbalance, pericarditis or cardiogenic shock, which are frequently seen before death. Patients were included even if they had a fatal second MI, provided that the initial MI could be distinguished anatomically and that an electrocardiogram was available from the period between the 2 infarcts. In such cases, only the size of the initial MI was considered. All electrocardiograms were analyzed by investigators blinded to the anatomic results.

The complete Selvester method¹⁶ (Figure 2) assigns points to apportion the damage in the 12 segments of the heart corresponding to the following distributions of the 3 major coronary vessels: left anterior descending—anteroseptal (1 to 3) and anterosuperior (4 to 6) segments; right coronary—inferior segments (7 to 9); and left circumflex—posterolateral segments 10 to 12.²¹ Points were accumulated from manual measurements of the QRS complexes in 10 electrocardiographic leads (I, II, aVL, aVF, V₁ to V₆). The Q and R durations were measured in milliseconds along the PR baseline and the amplitudes of the waveforms were measured in millivolts. In case of baseline shifts, the R wave was measured from the PR and the S from the ST segment, since the waveforms measured from their respective

baselines have been shown to most nearly maintain their control positions during ischemia.²² The anatomic evaluations of the simplified system¹⁰⁻¹² preceded the study by Wagner et al,²² and consequently, all amplitude measurements had been performed at the PR segment baseline. Electrocardiographic percent MI was estimated using the QRS score multiplied by 3, since each point was designed to represent approximately 3% infarction of the left ventricle,⁸ as proven in previous studies.¹⁰⁻¹²

The 37 criteria (maximum 29 points) of the simplified system were applied to determine electrocardiographic percent MI. The 17 additional criteria (Figure 2) which augment this system (maximum 32 points) were analyzed subsequently, and electrocardiographic percent MI was determined again for comparison with the simplified version. Each of the new criteria was evaluated in each location to determine whether it better estimated or overestimated the anatomic MI size established by the simplified system for each patient. Since many of the new criteria have been added to groups existing in the simplified system, they may be met but have neither positive nor negative effect on the anatomic-electrocardiographic MI size relation.

Statistical analysis: To measure the linear association between the anatomic and electrocardiographic percent MI, Spearman correlations were used. Unlike the previously used Pearson method,¹⁰⁻¹² this nonparametric method avoids the underlying assumption of normally distributed data and is therefore more appropriate.

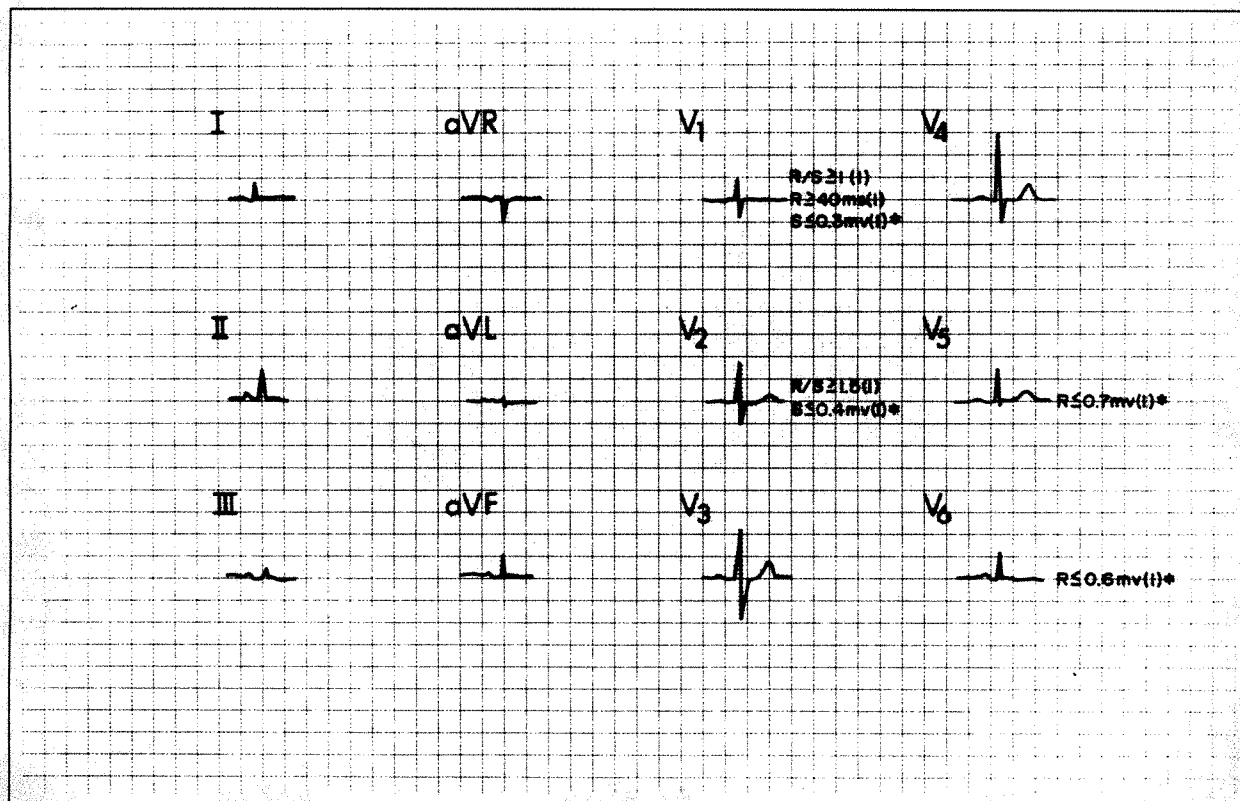


FIGURE 3. Twelve-lead electrocardiogram of a patient showing criteria met from both simplified and complete* versions of Selvester scoring system. * = new criteria.

TABLE I Anatomic Versus Electrocardiographic Results in the Selvester QRS Systems

Anatomic		Electrocardiographic							
Location	Mean % MI	Simplified System				Complete System			
		Mean % MI	r	R ²	p Value	Mean % MI	r	R ²	p Value
Anterior	23	17	0.92	0.85	0.0001	21	0.91	0.83	0.0001
Inferior	15	13	0.61	0.37	0.0003	14	0.60	0.36	0.0004
Postero-lateral	13	8	0.55	0.30	0.0121	11	0.70	0.49	0.0006

MI = myocardial infarction.

TABLE II Incidence of Improvement or Worsening of the Relation of Anatomic-Electrocardiographic Infarct Size

Lead	New Criteria (mv)	Total No. Times Met	Infarct Location								
			Anterior (n = 21)			Inferior (n = 30)			Posterolateral (n = 20)		
			+	-	no Δ	+	-	no Δ	+	-	no Δ
I	R ≤ 0.2	9	3	1	2	1	0	0	2	0	0
V ₁	Q or S ≥ 1.8	3	0	1	0	0	2	0	0	0	0
	R ≥ 1.0	1	0	0	0	0	0	1	0	0	0
	R ≥ 0.6	2	0	0	0	0	0	1	0	0	1
	Q and S ≤ 0.3	5	0	0	0	0	0	0	4	1	0
V ₂	RV ₂ ≤ RV ₁	18	2	1	14	0	0	0	1	0	0
	R ≤ 0.1	16	1	1	14	0	0	0	0	0	0
	R ≥ 2.0	1	0	0	0	0	1	0	0	0	0
	R ≥ 1.5	3	0	0	0	1	0	0	0	1	1
	Q and S ≤ 0.4	6	0	0	0	1	1	0	3	1	0
V ₃	R ≤ 0.2	21	2	1	15	0	2	0	1	0	0
V ₄	R ≤ 0.7	19	2	0	13	0	1	1	1	0	1
	Notched R	0	0	0	0	0	0	0	0	0	0
V ₅	R ≤ 0.7	14	2	0	9	0	1	1	1	0	0
	Notched R	0	0	0	0	0	0	0	0	0	0
V ₆	R ≤ 0.6	18	8	0	2	2	0	2	2	0	2
	Notched R	3	3	0	0	0	0	0	0	0	0

+ = improvement; - = worsening; no Δ = no change.

ate. Because multiple comparisons (6) were performed in relatively small numbers of patients, it was determined that a level ≤ 0.008 should be required to indicate significance for the above tests. Correlation coefficients resulting from use of the simplified versus the complete scoring systems were compared using a *t* test. Signed rank tests were used to compare the errors between each of the QRS scoring systems and anatomic results. A significance level ≤ 0.05 was chosen for the latter tests.

RESULTS

Seventy-one patients were included in the study: twenty-one had anterior, 30 had inferior and 20 had posterolateral MI. Fifty-eight (82%) patients were men (age range 28 to 78 years, mean 56), while 13 (18%) were women (age range 36 to 84 years, mean 63).

The mean anatomic percent size determined anatomically for all patients was 17.0%. Comparatively, the mean electrocardiographic percent MI was 12.9% using the simplified system and 15.0% using the complete system (difference not significant). Figure 3 shows an example of a patient with a posterolateral MI and a 27%

anatomic MI size. Using the simplified version, 3 QRS points (9% MI) were accumulated and the new criteria added 4 other QRS points (total, 21% MI).

Table I lists the statistical comparisons between the anatomic and electrocardiographic percent MI using the 2 systems for each MI location. The electrocardiographic percent MI using the simplified system differed from the anatomic percent MI by 24, 9 and 43% for the anterior, inferior and posterolateral infarct groups, respectively. The use of the 17 additional criteria narrowed these differences to 10, 1 and 20%, respectively, for the same groups.

Figure 4 shows the relation between anatomic and electrocardiographic percent MI using both the simplified and complete versions of the Selvester system in each MI location. Previous reports¹⁰⁻¹² showed the relation in these same patient populations using the Pearson method. This study indicated similar *r* values using both the simplified and complete systems for the anterior and inferior MI groups. For the posterolateral MI group, the *r* values were 0.55 ($p < 0.0121$) and 0.70 ($p < 0.0006$) using the simplified and complete versions, respectively. These 2 correlations were statistically differ-

ent from one another ($p = 0.036$). The error, defined as the difference between the complete version and anatomic result, was found not to be statistically significant.

Table II lists the 17 new criteria, the instances they were met and their effect on the relation of the anatomic-electrocardiographic percent MI. Six criteria rarely or never affected this relation at all. Five criteria involving small Q, R or S amplitudes improved the electrocardiographic estimate in various MI locations. The small R wave criteria in leads I, V_2 ($RV_2 \leq RV_1$) and V_6 were helpful in patients with all of the MI locations and led to overestimation in only 2 patients with anterior MI. The V_6 notched R performed similarly, but was never met in the absence of the V_6 small R criterion. The small Q and S criteria in both V_1 and V_2 improved the electrocardiographic estimate in 7 patients with posterolateral MI while overestimating anatomic size in 2 others. These 2 criteria rarely appeared in association with other MI locations.

Other criteria either improved or worsened the relation in different locations. The small R criteria in V_3 , V_4 and V_5 were helpful in 6 of those with anterior and 3 of

TABLE III Percent Infarction According to Electrocardiographic Segments in the Selvester Systems

Electrocardiographic		Simplified Version	Complete Version	
Region	Segment		Overlap*	Unique†
Anteroseptal	1	100	75	0
	2	100	50	0
	3	38	13	25
Anterosuperior	4	100	88	0
	5	100	50	0
	6	50	13	13
Inferior	7	100	63	0
	8	100	38	13
	9	100	0	0
Posterolateral	10	100	88	13
	11	100	75	25
	12	100	13	25

* New criteria that overlap with simplified version; † new criteria that are unique to complete version.

those with posterolateral MI while worsening the relation in only 1 with anterior MI. However, these criteria worsened the relation in 4 patients with inferior MI.

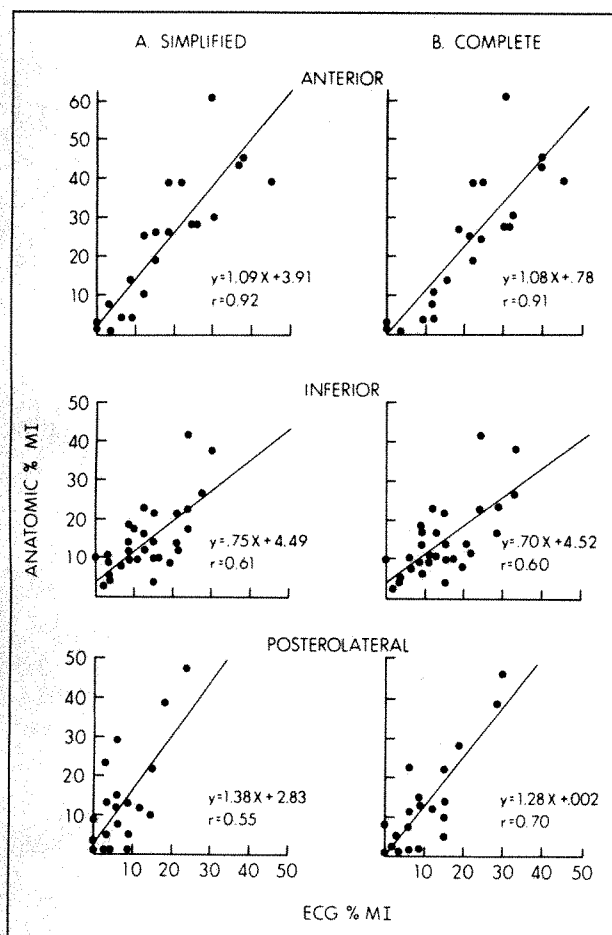


FIGURE 4. Correlations between anatomic and electrocardiographic infarct sizes using simplified and complete Selvester versions in each infarct location. Electrocardiographic infarct size = QRS score $\times$ 3. Linear relation lines for Spearman correlation are shown.

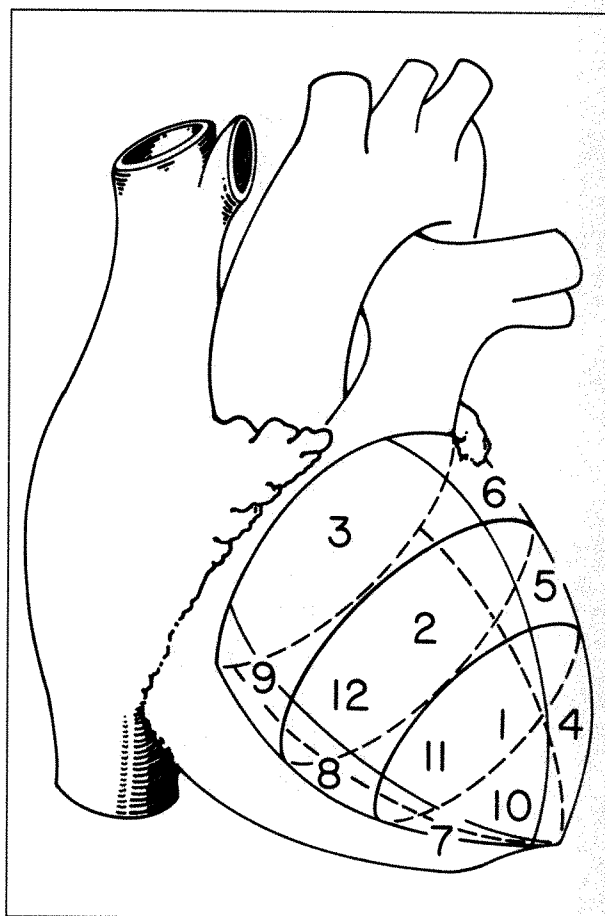


FIGURE 5. Diagrammatic representation of 12 segments of the heart, corresponding to distributions of 3 major coronary vessels, used for electrocardiographic evaluation. Segments 1 to 3, anteroseptal region; segments 4 to 6, anterosuperior region; segments 7 to 9, inferior region; segments 10 to 12, posterolateral region. Reproduced from Selvester et al⁸ with permission of the publisher.

The large Q or S amplitude in V_1 and the larger of the 2 R amplitudes in V_2 worsened the relation in 3 and 1 patients, respectively.

Figure 5 shows a diagrammatic representation of the 12 segments of the heart. The percent infarction depicted by the criteria in the simplified version, as well as the percent infarction represented by the additional criteria which either overlap with the simplified version or are unique to the complete system, are shown for each segment in Table III. Criteria in the simplified version are able to depict 100% infarction in most segments except for the anterosuperior and anterosuperior basal segments. Fourteen additional criteria in the complete version represent infarction that are already accounted for by the simplified version in all segments, except the inferior basal segment. However, 3 criteria are unique to the complete version and these are represented mainly in the entire posterolateral region, and the anterosuperior and anterosuperior basal and inferior middle segments.

DISCUSSION

The lesser capability of the simplified version of the scoring system to estimate MI size may be explained in terms of its own limitations.²¹ The major changes in R and S wave amplitude and/or notching in the QRS complexes that were apparent in the simulations and in clinical infarcts had not been included. Secondly, its maximally accumulated 29 points can only indicate infarction in 87% of the left ventricle. Finally, there is relative underrepresentation of the posterolateral and basal regions of the heart. These limitations, however, have been largely overcome by adding the amplitude and notching criteria to form the complete scoring system. The specificity of the added criteria proved to be acceptable ($\geq 95\%$) in a study of 500 normal subjects.¹⁶ Its maximum 32 points is capable of indicating MI in 96% of the left ventricle and 6 of the new criteria are specifically related to the posterolateral wall.

Reports of other investigators^{14,23-25} have pointed out that a taller R wave and decreased S wave in lead V_1 and decreased R amplitude in V_5 and V_6 may denote infarction in the posterior and lateral aspects of the left ventricle which are supplied by the left circumflex. Movahed et al,¹⁵ in a study of 31 patients with first infarction, showed inconsistent electrocardiographic changes in the presence of moderate to severe perfusion defects of the lateral and posterolateral walls. They suggested recording additional chest leads (V_7 to V_9) or upper left precordial and left axillary leads to disclose infarction in these areas not revealed by the standard 12-lead electrocardiogram.

This study is in agreement with previous reports¹⁰⁻¹² that the QRS scoring system and the anatomic methods have an excellent correlation for anterior infarcts and a lesser correlation for inferior infarcts. This may be due to the larger mean and greater range of infarct size in the anterior group. Since both simplified and complete versions of the QRS scoring system consider only 2 leads to indicate MI in the inferior region of the left ventricle, it is not surprising that there will be electrocardiographic underestimation of anatomic MI size. For

the anterior MI group, 30 criteria are distributed over 6 leads (V_1 to V_6). The posterolateral group benefits from having 6 added criteria in the complete version, 2 of which (small Q or S amplitude in V_1 and V_2) were found to be helpful. These resulted in significant improvement of the correlation coefficient from 0.55 to 0.70.

The criteria, which were introduced in the simplified version of the Selvester QRS scoring system, have been shown to attain a high level of performance regarding anterior infarction in several studies. Our study documents the improved ability of the complete Selvester scoring system to size infarcts in the posterolateral region of the left ventricle. It is hoped that future investigations using computer simulations based on the results of these anatomic studies will elucidate changes in the activation sequence caused by infarcts in the inferior myocardium. New criteria from these simulations, from other published studies,^{14,23-25} and from additional leads¹⁵ may further improve the ability of the electrocardiogram to estimate the size of acute and healed MIs.

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Comparison of the Effects of a Controlled-Release Formulation of Isosorbide-5-Mononitrate and Conventional Isosorbide Dinitrate on Exercise Performance in Men with Stable Angina Pectoris

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Thirty-three men with stable exercise-induced angina pectoris entered a randomized, double-blind, crossover study in which controlled-release isosorbide-5-mononitrate 60 mg once daily was compared with conventional isosorbide dinitrate 20 mg 3 times daily. Each drug was given for 2 weeks. Twenty-eight patients completed the study and data on exercise variables are available in 23 patients. Treatment with either drug resulted in significant antianginal effects, when measured 6 hours after a single dose and after 2 weeks of therapy compared with baseline placebo; however, there were significantly fewer signs of myocardial ischemia during treatment with isosorbide-5-mononitrate. There was no evidence of tolerance to either drug treatment but a significant attenuation of resting blood pressure (but not of exercise blood pressure) was observed with both drugs. Headache was the only clinically significant adverse event during therapy and it occurred more frequently in the isosorbide dinitrate treatment group ($p < 0.05$ vs placebo); 3 such patients had to withdraw from the study because of headache. Thus, once-daily, controlled-release isosorbide-5-mononitrate appears as effective as conventional isosorbide dinitrate 3 times daily in patients with stable angina pectoris. The once-daily administration is convenient and improves patient compliance.

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Oral isosorbide dinitrate is an effective antianginal drug.¹⁻³ However, it is subject to extensive first-pass metabolism,⁴ which limits its bioavailability to only 16 to 59%,⁵ and has a short plasma half-life. It is rapidly metabolized to pharmacologically active isosorbide-2-mononitrate and isosorbide-5-mononitrate.⁴ Isosorbide-5-mononitrate is nearly 100% bioavailable after oral administration and has a relatively long plasma half-life of 4 to 5 hours.^{6,7} To prolong the duration of its effects and provide a more convenient dosage schedule, a controlled-release formulation (Durules®) of isosorbide-5-mononitrate has been developed (Imdur®). This formulation produces effective daytime plasma concentrations and low levels at the end of the dosing interval (night). Such pharmacokinetic properties are considered necessary to avoid the development of tolerance,^{8,9} which nonetheless remains a concern. The present study compares the antianginal and antiischemic effects of controlled-release isosorbide-5-mononitrate 60 mg administered once daily with those of conventional isosorbide dinitrate 20 mg given 3 times daily in patients with stable angina pectoris. The effects of a single dose of each drug were compared with steady-state efficacy after 2 weeks of treatment to assess the development of tolerance.

METHODS

Patients: Thirty-three men were included. All had a history of stable exertional angina pectoris for 3 months and a positive exercise test (chest pain together with ≥ 1 mm of negative ischemic ST-segment change). All 28 patients who completed the study underwent coronary angiography, which revealed significant coronary artery disease, defined as $\geq 70\%$ stenosis of 1 major vessel. According to the New York Heart Association classification, 14 patients were in class III, 17 in class II and the remaining 2 patients in class I. Patient characteristics are listed in Table I.

Exclusion criteria: Reasons for exclusion from the study were: heart failure; myocardial infarction or coronary artery surgery within the previous 6 months; diastolic blood pressure > 100 mm Hg; atrioventricular block grade II or III or left bundle branch block; valvular heart disease; cardiac arrhythmias requiring drug treatment; systolic blood pressure < 100 mm Hg; insulin-dependent diabetes mellitus; nitrate intolerance;

drug (including alcohol) abuse or any other reason for suspecting poor compliance; and participation in other studies. All patients gave written informed consent and the study was performed according to the guidelines of the Declaration of Helsinki. The study was reviewed and approved by the Hospital Board, acting as the ethical committee.

Protocol: All antianginal medications and other drugs that can affect the cardiovascular system were discontinued at least 48 hours before the placebo run-in period; sublingual nitroglycerin was permitted for symptomatic relief, but not within 1 hour of exercise testing (Figure 1). Cardiac glycosides were withdrawn at least 1 week before the study began.

At the first visit a complete medical history was recorded and a physical examination was performed, including a standard 12-lead resting electrocardiogram. The patient started a 1-week single-blind placebo run-in period. Provided no exclusion criteria occurred and all inclusion criteria were fulfilled, the patients were randomly allocated (computer-generated in blocks of 4) to 2-week treatment with controlled-release isosorbide-5-mononitrate 60 mg (AB Hässle/Astra Cardiovascular) each morning followed by a 1-week placebo washout and 2-week treatment with conventional isosorbide dinitrate 20 mg 3 times daily, or vice versa. All tablets were of identical appearance and taste, and additional placebo tablets were administered during the isosorbide-5-mononitrate periods to maintain blindness. The tablets were taken at 8-hour intervals: at 9:00 A.M., 5:00 P.M. and 11:00 P.M.. At the end of each treatment period, repeat physical examinations and exercise tests were performed (Figure 1). Patients were asked to refrain from smoking on the day of exercise testing. The occurrence of anginal attacks and nitroglycerin consumption were recorded on diary cards. Tablet counts were performed at each visit to assess patient compliance.

Exercise testing: Treadmill exercise testing, using a modified Bruce protocol,¹⁰ was used. An electrocardiogram with at least 4 chest leads was recorded continu-

TABLE I Patient Characteristics

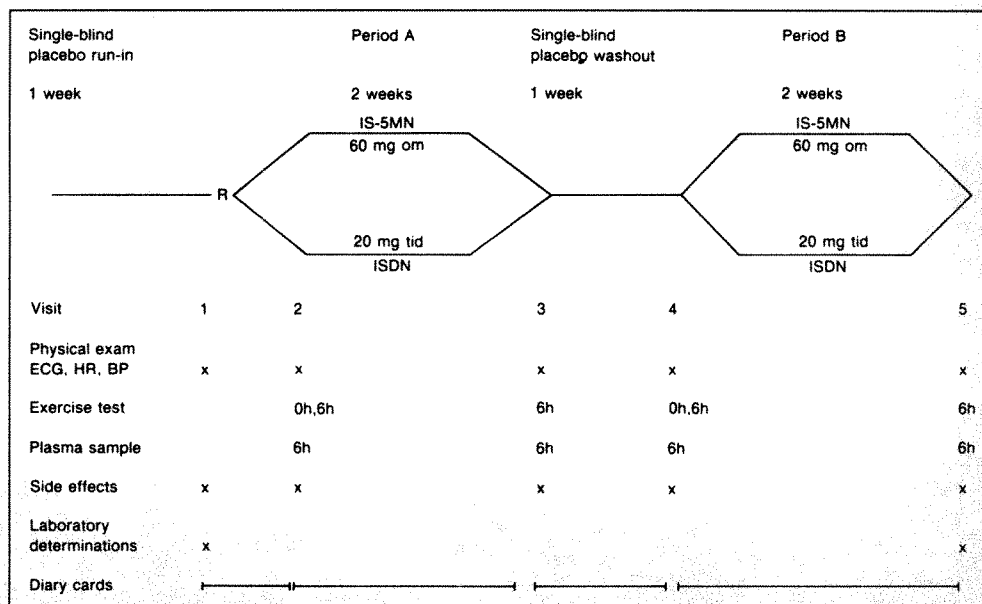
Mean age (yrs) (range)	51 (36-65)
Mean duration of angina (yrs) (range)	2.5 (0.25-11)
Extent of coronary artery disease	
Single-vessel	11
Double-vessel	4
Triple-vessel	12
Triple-vessel plus left main coronary artery	1
Cigarette smokers	15
Previous myocardial infarct (%)	16 (48)
Systemic diastolic pressure 96-99 mm Hg (%)	7 (21)
Total serum cholesterol >250 mg/dl (%)	12 (36)
Claudication (%)	2 (6)
Diabetes mellitus (%)	2 (6)

ously during and up to 6 minutes after the exercise. The exercise test was started at low speed (1.7 miles/hour) without elevation for 3 minutes. Both speed and elevation were increased gradually every 3 minutes. During and up to 6 minutes after exercise, the patients rated chest pain according to Borg's 10-point scale.¹¹ Exercise was terminated at a point that would ordinarily have stopped the patient from continuing because of the severity of anginal symptoms, fatigue or leg discomfort. Time to onset of chest pain, total exercise duration, time to appearance of 1-mm ST-depression and the reason for terminating the exercise test were all recorded. These tests were performed at the end of the placebo run-in and washout periods, 6 hours after the first dose of each active treatment and at the end of the 2 active treatment periods (6 hours after the morning dose).

Blood pressure and heart rate: Blood pressure and heart rate were measured after 5 minutes in the supine position and after 1 minute in the standing position. During the exercise test, heart rate was recorded every minute and systolic blood pressure was measured every third minute.

Adverse events and laboratory variables: At all clinic visits adverse events were recorded by open questioning. Patients were asked to classify symptoms ac-

FIGURE 1. Study design. BP = blood pressure; ECG = electrocardiogram; h = hour(s); HR = heart rate; ISDN = isosorbide dinitrate; IS-5MN = isosorbide-5-mononitrate.



cording to onset, duration and severity (1 = mild; 2 = moderate; 3 = severe). If severe adverse events occurred during active treatment periods, therapy was discontinued. Laboratory variables (routine blood chemistry and urine analysis) were examined at the start and end of the study.

Statistical analysis: Unless stated otherwise, values are mean $\pm$ standard deviation. For each studied effect, individual values were assumed to constitute a random sample from a multivariate distribution and were considered to be normal for exercise and hemodynamic variables, and nonnormal for anginal attacks, nitroglycerin usage, patient preference and adverse events. A model with period, treatment and carryover effects was used. Three main hypotheses were assessed for each variable under investigation. Was there a treatment effect after a single dose and after 2 weeks' therapy? Was there any difference between isosorbide-5-mononitrate and isosorbide dinitrate? Was there any difference between the effect after a single dose and after 2 weeks' treatment (i.e., did tolerance occur)?

Each hypothesis was tested by use of a univariate repeated measures analysis of variance model. Standard methods were used for normally distributed variables.

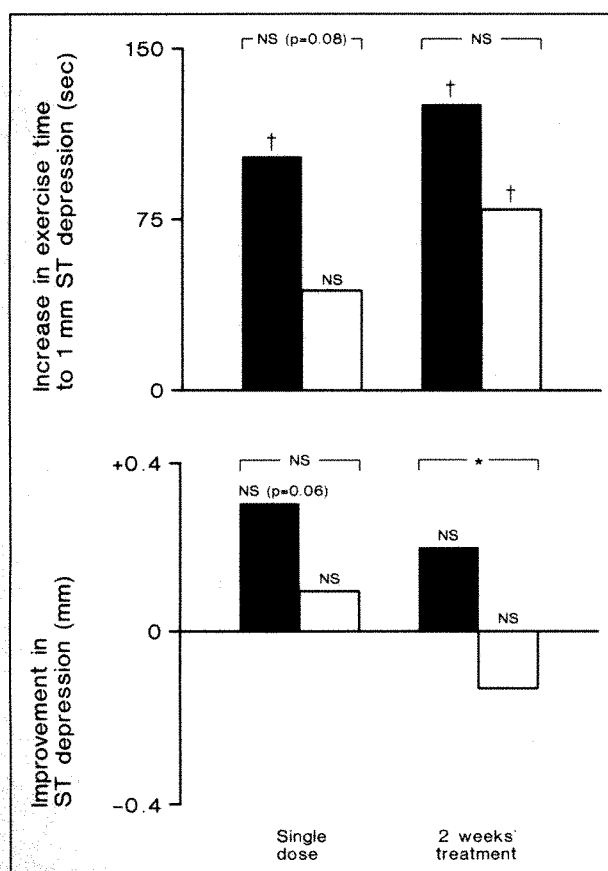


FIGURE 2. Increase in exercise time to 1 mm ST-segment depression and improvement in ST-segment depression (both compared with preceding placebo values) after a single dose of drug or after 2 weeks' treatment with controlled-release isosorbide-5-mononitrate 60 mg once daily (closed square) or conventional isosorbide dinitrate 20 mg 3 times daily (open square). * Statistically significant difference between active treatment; † statistically significant difference from preceding placebo period. NS = difference not significant.

For nonnormally distributed variables, nonparametric tests were applied: these were the Mann-Whitney and Wilcoxon signed-rank tests, depending on the variable under investigation. Patient preference was assumed to follow a multinomial distribution where the probability of choosing 1 of the 4 treatment periods was evaluated by use of the chi-square test. This was checked by paired binomial tests in cases of statistical significance. A 2-tailed p value <0.05 was considered significant.

RESULTS

Of the 33 patients, 5 did not complete the trial; 2 developed unstable angina pectoris (1 during the placebo run-in and 1 during treatment with isosorbide dinitrate first leg) and 3 others developed severe headaches (not responsive to acetaminophen during treatment with isosorbide dinitrate) (2 in first leg and 1 in second leg). In addition, 5 patients who completed the study failed to take their morning dose of medication at the end of the first period of active treatment and had to be excluded from the exercise performance and hemodynamic analyses listed in Table II. These patients were, however, included in all other analyses.

Exercise duration: Time to onset of chest pain was significantly increased by both drugs, and total exercise time by isosorbide-5-mononitrate, both after a single dose and after 2 weeks' therapy. However, total exercise time was significantly increased only after 2 weeks' therapy with isosorbide dinitrate ($p < 0.05$). For both nitrates, the effects on exercise performance seemed to be better after 2 weeks' continuous therapy than after a single dose, and for isosorbide-5-mononitrate the increase in total exercise time was significant ($p < 0.05$). An increase in total exercise time of ≥ 30 seconds was experienced by 18 of 23 patients (78%) receiving isosorbide-5-mononitrate for 2 weeks and by 16 of 23 (70%) receiving isosorbide dinitrate.

Time to appearance of ST depression: Table II lists the effects of each drug. The exercise time until 1 mm ST depression was longer after treatment with isosorbide-5-mononitrate than after isosorbide dinitrate (Figure 2); the differences, however, did not reach the level of significance ($p = 0.08$ after a single dose). Similarly, isosorbide-5-mononitrate produced a more pronounced improvement in maximal ST depression and this was statistically significant ($p < 0.05$) after 2 weeks' therapy (Figure 2).

Hemodynamic effects at rest: There were no statistically significant differences in resting recumbent blood pressure and heart rate (Table II) and standing measurements (data not shown) between treatments. Notably, there was a marked attenuation of the effect on blood pressure after 2 weeks' therapy with both controlled-release isosorbide-5-mononitrate and conventional isosorbide dinitrate tablets.

Hemodynamic effects during exercise: There were no significant differences between treatments on any of the hemodynamic variables measured (Table II), except for heart rate-blood pressure product at the onset of pain after 2 weeks' therapy, which was significantly higher after isosorbide dinitrate than after isosorbide-5-mononitrate ($p < 0.05$).

TABLE II Hemodynamic and Exercise Performance Values After First Dose and Two Weeks' Treatment with Controlled-Release Isosorbide-5-Mononitrate and Conventional Isosorbide Dinitrate

Parameter	Isosorbide-5-Mononitrate 60 mg om			Isosorbide Dinitrate 20 mg tid		
	Placebo	Single Dose	2 Weeks	Placebo	Single dose	2 weeks
Time to chest pain (s)	521 ± 227	605 ± 180*	658 ± 185 [†]	544 ± 209	630 ± 159 [†]	672 ± 220 [‡]
Total exercise time (s)	540 ± 213	617 ± 167*	687 ± 179 [†]	600 ± 202	635 ± 161	679 ± 212*
Time to 1 mm ST-depression (s)	432 ± 210	533 ± 204*	557 ± 202 [†]	477 ± 208	520 ± 192	556 ± 241*
Maximum ST-depression (mm)	1.8 ± 1.0	1.4 ± 0.9	1.6 ± 0.9	1.6 ± 1.0	1.5 ± 0.8	1.7 ± 0.8
Hemodynamics at rest						
Supine systolic BP (mm Hg)	133 ± 19	116 ± 17 [‡]	130 ± 17	133 ± 17	119 ± 17 [‡]	129 ± 14
Supine diastolic BP (mm Hg)	84 ± 8	76 ± 11 [‡]	81 ± 12	81 ± 8	76 ± 10 [†]	83 ± 12
Supine HR (beats/min)	67 ± 8	76 ± 11 [‡]	73 ± 13 [†]	69 ± 11	75 ± 14*	71 ± 11
Hemodynamics during exercise						
At onset of pain						
Systolic BP (mm Hg) (n = 17)	178 ± 21	178 ± 33	181 ± 28	170 ± 19	174 ± 26	185 ± 19 [†]
HR (beats/min) (n = 21)	130 ± 24	144 ± 24*	142 ± 24	130 ± 25	145 ± 23 [‡]	142 ± 23*
HR × BP (beats/min · mm Hg) (n = 17)	24,059 ± 5,625	26,021 ± 7,557	25,401 ± 5,735	22,238 ± 5,761	25,646 ± 6,482 [†]	27,081 ± 4,755 [‡]
At end of exercise						
Systolic BP (mm Hg)	176 ± 19	176 ± 31	182 ± 27	178 ± 20	176 ± 28	181 ± 19
HR (beats/min)	132 ± 24	145 ± 22 [†]	143 ± 24	137 ± 23	146 ± 23*	142 ± 24
HR × BP (beats/min · mm Hg)	23,400 ± 5,332	25,670 ± 6,731*	25,979 ± 5,923	24,295 ± 4,651	25,759 ± 5,894	25,817 ± 5,039

Values are mean ± standard deviation from 23 patients unless otherwise stated.

* p < 0.05; [†] p < 0.01; [‡] p < 0.001 vs preceding placebo treatment period.

BP = blood pressure; HR = heart rate; om = every morning; tid = 3 times daily.

Anginal attacks and nitroglycerin consumption:

These parameters were very low and there were no statistically significant differences between active treatment and placebo periods, or between the active treatments.

Patient preference: At the end of the trial 17 patients expressed a preference for active treatment, whereas only 1 patient preferred placebo (p < 0.05); 10 patients had no preference. Of the 17 patients preferring active therapy, 9 chose isosorbide-5-mononitrate, 7 preferred isosorbide dinitrate and 1 had no preference for either drug.

Adverse events: During treatment with isosorbide dinitrate 3 patients withdrew from the study because of severe headache unrelieved by acetaminophen, 1 patient after having received isosorbide-5-mononitrate in the previous period. Headache was the only clinically significant adverse experience, and was reported by 10 of 28 patients during treatment with isosorbide-5-mononitrate (not significant compared with placebo; 1 severe, 3 moderate and 6 mild) and 15 of 28 patients during treatment with isosorbide dinitrate (p < 0.05 compared with placebo; not significant compared with isosorbide-5-mononitrate; 1 severe, 10 moderate and 4 mild).

No clinically significant changes in hematology, blood chemistry or urine analysis were observed. Mean aspartate aminotransferase values increased slightly but significantly (p < 0.05) by the end of the trial but remained within the normal range.

DISCUSSION

Controlled-release isosorbide-5-mononitrate 60 mg in the morning, compared with preceding placebo, prolonged total exercise time and the duration of exercise before chest pain, and reduced signs of myocardial ischemia in patients with documented coronary artery disease (positive exercise test and angiography). These ef-

fects were measured 6 hours after administration and occurred after a single dose and after 2 weeks' treatment. Similar findings have been reported in other studies.^{12,13} Isosorbide dinitrate produced comparable improvement in exercise performance but was significantly less effective in reducing signs of myocardial ischemia. Total exercise duration during run-in and washout periods was similar, indicating absence of training effect.

The possible development of tolerance to nitrate therapy is an area of concern,^{14,15} especially during long-term administration.¹⁶⁻¹⁹ Recent opinion suggests that tolerance may be avoided by allowing the nitrate plasma concentration to decrease for some part of the dosing interval.^{19,20} In this study, exercise testing was performed 6 hours after nitrate administration because it is possible to detect tolerance, if it has occurred, at this time.²¹ Exercise performance was if anything further improved after 2 weeks as compared with the first dose testing. In view of the absence of training effect, these findings are in agreement with lack of tolerance development. The lack of tolerance development after treatment with 60 mg isosorbide-5-mononitrate once daily is important in view of the reported efficacy duration of at least 12 hours with this dosage.²²

There were no significant differences between isosorbide-5-mononitrate and isosorbide dinitrate in resting and exercise hemodynamic variables except for heart rate blood pressure product at the onset of angina after 2 weeks' therapy, which was greater during treatment with isosorbide dinitrate. Interestingly, there was a significant attenuation of resting, but not exercising, blood pressure after 2 weeks' treatment with isosorbide-5-mononitrate and isosorbide dinitrate. Heart rate blood pressure product, which can be used as a rough estimate of myocardial oxygen consumption, was significantly increased by isosorbide dinitrate (compared with placebo) at onset of angina. Isosorbide-5-mononitrate had a less-

er effect on heart rate blood pressure product during exercise, and caused a small increase at the peak exercise. This may indicate less myocardial oxygen consumption during treatment with isosorbide-5-mononitrate compared with isosorbide dinitrate treatment.

Both treatment regimens were generally well tolerated and the only clinically significant adverse event was headache.

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Clinical Significance of Silent Ischemia in Unstable Angina Pectoris

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In a prospective study the significance of silent ischemia was evaluated in 66 patients with a clinical diagnosis of unstable angina (no requirement for reversible ST-T changes during pain on 12-lead electrocardiograms before entry), and the results of continuous 2-channel electrocardiographic (ECG) recordings, begun within 24 hours of admission, were compared with other clinical and ECG predictors of adverse outcome. Ischemic changes were detected in 7 patients (11%) during a mean of 41 hours of recording. There were 37 episodes of transient ST-segment change (16 ST elevation, 21 ST depression) of which 11 (30%) were symptomatic and 26 (70%) were silent. All 7 patients had at least 1 silent episode and 5 also had symptomatic episodes during the recording but only 2 patients had exclusively silent episodes. During a mean follow-up of 13.3 months, 3 patients died, 5 had a nonfatal myocardial infarction and 32 required revascularization. Although transient myocardial ischemia during the continuous ECG recording, whether silent or symptomatic, was a specific predictor of subsequent nonfatal myocardial infarction or death (specificity 92%), its sensitivity for these events was low (25%). In contrast, recurrent rest pain (≥ 1 episode) occurred in all patients with these serious adverse events (sensitivity 100%, specificity 49%). Transient ischemia occurs infrequently during continuous ECG recordings in patients with unstable angina not selected by reversible ST-T changes on a 12-lead electrocardiogram at entry. Recurrent rest pain after hospital admission is a more sensitive predictor of serious events in this group.

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Recurrent rest pain during hospitalization is an important adverse prognostic factor in patients with unstable angina.¹⁻³ As most episodes of myocardial ischemia are not accompanied by pain,⁴⁻¹¹ recurrent silent ischemia during continuous electrocardiographic (ECG) recordings has been suggested to be a better predictor of early^{7,8} and late⁹ outcome than rest pain. Most studies have been restricted to patients with transient changes on 12-lead electrocardiograms during rest pain^{5,7,9,10} (i.e., 20% of medically treated patients with unstable angina).^{12,13} These patients may not be representative of those admitted to coronary care units with the clinical diagnosis of unstable angina. We determined the prevalence of ischemia during continuous ECG recordings in patients with the clinical diagnosis of unstable angina, and compared its prognostic significance with clinical predictors such as recurrent chest pain.

METHODS

Patient selection: Patients admitted to the coronary care unit with a clinical diagnosis of unstable angina were included in the study if they were <75 years old and the resting electrocardiogram was interpretable for ischemia (absence of left bundle branch block, left ventricular hypertrophy with ST-segment changes or resting ST depression >1 mm). Patients in whom the continuous ECG recording could not be begun within 24 hours of admission, or who declined to participate in the study, were excluded. During a 10-month period, 69 patients fulfilled these criteria and had continuous ECG recordings performed: 3 patients in whom recordings were begun evolved an acute myocardial infarction (creatinine kinase >2 times upper normal) within 24 hours of admission and were excluded from further analysis. Thus, 66 patients form the basis of this study.

Definition of unstable angina: Unstable angina was regarded as either: (1) angina at rest—angina occurring without provocation by physical or emotional stress (62 patients) or (2) progressive effort angina—angina either of new onset or superimposed on a prior history of stable angina of sufficient severity to warrant admission to the coronary care unit (32 patients, including 7 with progressive angina exclusively and 25 with both progressive effort angina and rest angina as defined previously). Additional criteria such as a prior history of coronary artery disease or reversible ischemic ECG changes during chest pain were not required for the diagnosis of unstable angina.

Patient management: All patients received standard medical therapy for unstable angina, which included bed rest, oral or transcutaneous nitrates, or both, calci-

TABLE I Comparison of Clinical, ECG and Angiographic Characteristics of Patients With and Without Ischemia During Continuous ECG Recordings

	Ischemia (n = 7)	No Ischemia (n = 59)	p Value
Mean age (yrs)	60 ± 14	56 ± 10	NS
Sex (M:F)	5:2	43:16	NS
Cigarette smokers (past/present) (%)	4 (57)	41 (69)	NS
Systemic hypertension (>140/90 mm Hg) (%)	2 (29)	30 (51)	NS
Diabetes mellitus (%)	1 (14)	9 (15)	NS
Peripheral or cerebrovascular disease (%)	3 (43)	11 (19)	NS
Cholesterol >6 mmol/liter (%)	6 (86)	48 (68)	NS
Prior AMI (%)	2 (29)	21 (36)	NS
Prior stable angina pectoris (%)	6 (86)	30 (51)	0.08
Evolutionary T wave changes (%)	3 (43)	10 (17)	NS
Minor elevations of CK (%)	1 (14)	7 (12)	NS
Rest pain after admission (%)	6 (86)	31 (53)	0.1
Reversible 12-lead ECG changes (%)			
ST elevation	0 (—)	0 (—)	
ST depression	3 (43)	8 (14)	<0.05
T wave changes	2 (29)	4 (7)	0.06
Total ST/T changes	3 (43)	10 (17)	0.1
Coronary angiography (%)	7 (100)	43 (73)	NS
Normal/minor (<50%) disease	0 (—)	6 (10)	NS
3-vessel/left main disease	5 (71)	14 (24)	<0.05
No. coronary arteries with ≥50% diameter reduction	3 ± 1	2 ± 1	<0.05

AMI = acute myocardial infarction; CK = creatine kinase; ECG = electrocardiographic; NS = not significant.

um antagonists (41 patients), β blockers (48 patients) and intravenous nitrates (12 patients) or heparin (20 patients). Twelve-lead electrocardiograms were recorded routinely in all patients in the emergency department, on arrival in the coronary care unit, during recurrences of pain and when pain free, and before discharge. Acute myocardial infarction was excluded by serial plasma creatine kinase and creatine kinase-MB isoenzyme determinations. Recurrences of rest pain after admission were recorded on a specially designed pain chart.

All electrocardiograms recorded during hospitalization were examined and coded for pathologic Q waves,¹⁴ ST-segment elevation, ST depression, T-wave flattening or inversion. Reversible ischemic ECG changes were defined as ST-segment elevation ≥ 0.5 mm, downsloping or horizontal ST depression ≥ 0.5 mm measured 80 ms after the J point or T-wave flattening, inversion or pseudonormalization occurring with pain and resolving after pain.¹⁵ Historical data, details of events and symptom status in the hospital and during follow-up, together with ECG, cardiac enzyme and angiographic data, were entered in a computerized database.

Continuous electrocardiographic recording and analysis: ECG recordings were begun <24 hours after admission using a 2-channel amplitude modulated reel-to-reel Holter recorder (Delmar Avionics Electrocardiograph model 445B or Scola Alta III). Two bipolar monitoring leads (CM₃ and CM₅) were used, as this combination has been shown to have high sensitivity for

the detection of ischemic ST-segment change during ambulatory ECG monitoring.¹⁶ All recordings were calibrated with 1 mV square wave signals. At the beginning of each recording, 2 minutes of electrocardiogram were recorded with patients in the supine, right and left lateral, sitting and standing positions to detect positional ST-segment changes.¹⁷ Patients were instructed to press the event button during any symptoms and to record this in a diary. After 24 hours the tape was replaced to extend the total recording period to approximately 48 hours. At the end of the recording period patients were interviewed to check whether any symptoms had occurred.

Recordings were analyzed by a modification of the compact analog technique.¹⁸ Tapes were replayed on a standard Holter analysis system at 240 times real time, the recording transferred to a frequency modulated reel-to-reel recorder at high speed and replayed on an ink jet recorder in compressed format (30 times real time), or real time (paper speed 20 mm/s). An ischemic episode was defined as ≥ 1 mm horizontal or downsloping ST depression or ST elevation ≥ 1 mm lasting ≥ 1 minute. We previously validated this recording system using both simulated and real ECG signals and compared the ST-segment level and slope recorded using the Holter equipment with those recorded simultaneously using a standard ECG recorder. There was a good correlation between the ECG recorder and the Holter recorder for both ST-segment displacement 80 ms beyond the J point ($r = 0.98$) and ST-segment slope ($r = 0.87$). The compact analog technique detected simulator-generated ST-segment shifts >0.5 mm lasting >0.5 minute.

The number and duration of episodes of ischemia during the Holter recording, the occurrence of symptoms and the total duration of recording were noted for each patient. The attending cardiologists were unaware of the results of the continuous ECG recordings so that medical management was not influenced by these data.

Follow-up: Patients were interviewed at 4 months and 1 year (mean 13.3 ± 1.9 months) after discharge by one of the investigators. During interviews, they were asked specifically whether rest angina had recurred, whether they had required readmission to hospital for chest pain or coronary revascularization procedures (coronary angioplasty or bypass surgery). Causes of death were determined by interview of relatives and physicians. Follow-up was 100% complete.

Statistical analysis: Comparison between groups of continuous variables was performed using unpaired *t* tests. Differences in proportions were examined using the conditional binomial exact test, as appropriate for a 2×2 contingency table with small expected frequencies in ≥ 1 cell.^{19,20} A *p* value <0.05 was considered significant.

RESULTS

Holter recordings, clinical and angiographic data: During a total of 2,706 hours of continuous ECG recordings (mean 41 ± 11 hours/patient, range 16 to 54 hours), episodes of ischemic ST-segment change were

found in 7 patients (11%). A total of 37 ischemic episodes (mean 5/patient) were detected, 16 with ST elevation and 21 with ST depression. Eleven (30%) were symptomatic and 26 (70%) were silent. All patients with ischemic episodes during the recording had at least 1 silent episode: 2 of the 7 patients had exclusively silent episodes while the remaining 5 had pain during some of the ischemic episodes. There were no differences in age, sex, smoking history, diabetes, hypercholesterolemia or prior history of myocardial infarction between patients with and without ischemic episodes but patients with ischemic episodes had more extensive coronary disease (Table I).

Thirty-seven patients had ≥ 1 recurrence of ischemic pain at rest after admission to hospital. Rest pain recurred < 24 hours after admission in 20 patients and < 5 days in all 37. Six of 7 patients with ischemia during continuous ECG recordings had a recurrence of rest pain during hospitalization. The other patient had exclusively silent ischemia during the continuous electrocardiogram and no recurrence of rest pain in hospital. Angiographic severity of coronary disease was similar in patients whether they had recurrences of rest pain (mean number of diseased vessels $\geq 50\%$ stenosis 1.8 ± 1) or not (2.2 ± 1 vessels, $p = 0.2$).

Reversible ST/T changes were documented on a 12-lead electrocardiogram recorded during rest pain in 13 patients (20%), 11 of whom had transient ST-segment depression (Table I). Three of 7 patients (43%) with ischemia during continuous ECG recordings had reversible ST depression on a 12-lead electrocardiogram during pain compared to only 8 of 59 (14%) of those without ischemia during continuous ECG recordings ($p < 0.05$, Table I).

Clinical outcome: During a mean follow-up of 13.3 months, 5 patients had a nonfatal myocardial infarction and 3 patients died (2 fatal myocardial infarctions, 1 death immediately after bypass surgery) (Table II). Fourteen patients were readmitted with unstable angina. Only 3 of these events (1 cardiac death, 2 readmissions with unstable angina) occurred after the initial follow-up at 4.5 months. Revascularization by either coronary angioplasty (3 patients) or bypass surgery (29 patients) was performed in 32 patients (48%). There was a trend to a greater incidence of nonfatal myocardial infarction or death in patients with ischemia during continuous ECG recordings (29 vs 10%) that was not statistically different ($p = 0.16$). All 7 patients with ischemia during continuous ECG recordings required revascularization, compared to 42% (25 of 59) of the patients without ischemia during the recording ($p < 0.005$).

Prediction of major events: Of 7 patients with transient ischemia during the Holter recording, 2 had a major event (1 death, 1 nonfatal infarction). Despite this relatively high event rate (29%), ischemia during continuous ECG recording was an insensitive (2 of 8 events, 25%) although highly specific (92%) predictor of death or nonfatal infarction. We compared the prognostic value of ischemia during continuous ECG recordings with a series of clinical and other ECG descriptors that

TABLE II Events During the Study Period: Comparison of Patients With and Without Ischemia During Continuous ECG Recordings

	Ischemia (n = 7)	No Ischemia (n = 59)	p Value
Adverse events (%)			
Nonfatal AMI	1 (14)	4 (7)	NS
Cardiac death	1 (14)	2 (3)	NS
Readmission with UAP	1 (14)	13 (22)	NS
Nonfatal AMI/death	2 (29)	6 (10)	NS
Recurrent UAP/nonfatal AMI/death	2 (29)	18 (31)	NS
Revascularization (%)			
Coronary angioplasty	1 (14)	2 (3)	NS
Coronary artery surgery	6 (86)	23 (39)	< 0.02
Total revascularized	7 (100)	25 (42)	< 0.005

UAP = unstable angina pectoris; other abbreviations as in Table I.

included age, sex, current smoking, prior myocardial infarction, transient ECG changes during pain and recurrent rest pain after hospitalization. The only descriptor that was present in a significantly greater proportion of patients with death or nonfatal infarction was recurrent rest pain during hospitalization, which occurred in all 8 patients with major events (sensitivity 100%, specificity 49%).

DISCUSSION

Incidence of transient myocardial ischemia in unstable angina: Transient episodes of ST-segment change during Holter recordings begun within 24 hours of admission occurred in 11% of our patients, which is lower than the previously reported incidence (23 to 66%).⁴⁻¹⁰ Our patients were selected because of chest pain only and this may explain the difference between this and previous studies where pain and ST changes on a 12-lead electrocardiogram were the entry criteria.^{5,7,9,10} Using pain and ST changes as the entry criteria would select patients more likely to have transient ischemia during continuous ECG recordings,⁸ who may not be representative of patients with unstable angina usually admitted to the coronary care unit because of rest pain. This selection bias would increase estimates of the incidence of transient ischemia. If patients without transient changes on 12-lead electrocardiograms during pain had been excluded from our study, 80% would not have been monitored and, more importantly, most patients (6 of 8) who had a nonfatal myocardial infarction or died would have been excluded.

Prognostic significance of transient myocardial ischemia during Holter recordings: The incidence of death or nonfatal infarction was 12% during a mean follow-up of 13.3 months, which is similar to previous studies.^{11,21} Patients with transient myocardial ischemia during the continuous ECG recording showed a nonsignificant trend to increased risk of nonfatal myocardial infarction or death that was similar in magnitude to other studies.⁶⁻⁹ The incidence of 3-vessel or left main coronary disease was higher (71 vs 24%), and revascularization was performed more frequently (100 vs 44%) in patients with ischemia during continuous ECG re-

cordings. Although the endpoint of revascularization is of secondary importance, it may have favorably influenced the outcome in these patients.

Comparison with rest pain: In patients with unstable angina, symptoms have been used traditionally to guide therapy and to identify patients at high risk of adverse outcome. Previous studies comparing the prognostic value of recurrent rest pain with silent ischemia only considered symptoms that occurred during the continuous ECG recording and not recurrent rest pain before or after the recording.⁷⁻⁹ In the present study, as is usual clinical practice, we considered all episodes of rest pain during hospitalization. This predicted all 8 major events, in contrast to 2 events predicted by ischemia on continuous ECG recordings.

Clinical implications: Our findings are consistent with previous studies showing that transient myocardial ischemia during continuous ECG recordings is an adverse prognostic factor in unstable angina, but the clinical relevance depends on patient selection. When patients with unstable angina are observed to have transient ischemic changes on a 12-lead electrocardiogram during pain, the incidence of ischemia during continuous recordings is likely to be high, as previously reported⁶⁻⁸ and supported by our findings. If continuous ECG monitoring for ischemia is extended to the general patient population admitted to the coronary care unit with the clinical diagnosis of unstable angina, not selected because of ST changes on 12-lead electrocardiograms, the incidence of transient myocardial ischemia appears to be much lower. In these patients, recurrence of rest pain would seem to identify those with a poor prognosis more effectively.

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Risk Stratification of Single or Double Vessel Coronary Artery Disease and Impaired Left Ventricular Function Using Exercise Radionuclide Angiography

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Patients with 3-vessel coronary artery disease (CAD) and normal left ventricular (LV) function have a worse prognosis if they manifest ischemia during exercise testing. The present study determines if exercise radionuclide angiography can aid in the risk stratification of patients with 1- or 2-vessel CAD and impaired LV function (ejection fraction <50%). Sixty-five consecutive patients with these findings were followed for a median duration of 24 months (range 12 to 49). Eleven of the 65 patients (17%) had severely ischemic exercise radionuclide angiograms, defined as: a decrease in ejection fraction with exercise; ≥ 1.0 mm of ST-segment depression; and peak exercise workload ≤ 600 kg-m/min.

During follow-up 11 patients had initial significant cardiac events: 4 cardiac deaths, 1 cardiac arrest, 4 myocardial infarctions and 2 bypass or angioplasty procedures for unstable angina ≥ 3 months after the exercise study. Four of 11 patients (36%) with severely ischemic exercise radionuclide angiograms had events, compared to 7 of 54 patients (13%) without ischemic radionuclide angiograms. Event-free survival at 18 months was 73% for patients with severe exercise ischemia versus 92% for those without ischemia ($p < 0.05$). Univariate analysis showed that severe ischemia on radionuclide angiography was the only variable of several tested that significantly predicted future cardiac events (chi-square = 8.16, $p < 0.005$). Among patients with 1- or 2-vessel CAD and impaired resting LV function, severe ischemia on exercise radionuclide angiography identifies a subgroup at high risk for future cardiac events.

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For patients with coronary artery disease (CAD), the 2 major determinants of survival are the anatomic extent of disease and global left ventricular (LV) function.¹⁻⁴ The Coronary Artery Surgery Study showed that patients with 3-vessel CAD and impaired resting LV function have a worse prognosis when treated initially with medical management compared to surgery.⁵ Additional studies have demonstrated that patients with 3-vessel CAD and normal LV function are at higher risk if they demonstrate ischemia during exercise testing.⁶⁻¹⁰ Few studies have examined whether exercise modalities can aid in risk stratification of other subgroups of patients with CAD. Since the European Coronary Surgery Study⁶ only included patients with normal LV function and the Coronary Artery Surgery Study⁵ contained relatively few patients with either 1- or 2-vessel CAD and impaired LV function, there is limited data from the randomized trials regarding prognosis in this subset of patients. Mazzotta et al¹¹ have recently reported that a group of these patients who were asymptomatic or mildly symptomatic could be identified as low or high risk on the basis of exercise radionuclide angiography. The present study determines if a more symptomatic group of patients with 1- or 2-vessel CAD and impaired resting LV function are at increased risk if they manifest ischemia during exercise radionuclide angiography.

METHODS

Study group: The study group consisted of a consecutive series of patients with known or presumed CAD who underwent both exercise radionuclide angiography and coronary angiography and satisfied the following criteria: resting radionuclide LV ejection fraction <50%; coronary angiography within 3 months of exercise testing; 1- or 2-vessel CAD (using the definitions of the Coronary Artery Surgery study¹²); no prior history of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty; initial medical therapy following radionuclide angiography and coronary angiography; and absence of left bundle branch block.

The study group consisted of 65 patients (54 men, 11 women) whose mean age was 59 years (range 36 to 77). Fifty-seven patients had a history of myocardial infarction. Thirty-three had 1-vessel and 32 had 2-vessel CAD. At the time of exercise testing, 49 patients were taking at least 1 antianginal medication, including long-

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TABLE I Clinical and Exercise Test Variables for Patients With and Without Ischemic Exercise Radionuclide Angiograms

Variable	Ischemic RNA*		Nonischemic RNA*	
	No.	Percent	No.	Percent
Clinical				
Mean age (yrs)	64		58	
Male sex	11	100	43	80
Prior myocardial infarction	10	91	47	87
Postinfarction rehab study	1	9	4	7
Functional class (NYHA)				
0 to II	7	64	27	50
III to IV	4	36	27	50
Systemic hypertension†	5	46	23	43
Hyperlipidemia‡	5	46	23	43
Diabetes	2	18	6	11
Cigarette smoking	9	82	44	82
Treatment with β blockers	3	27	25	46
Exercise testing				
Peak workload	600		600	
(kg-m/min, median)				
Peak exercise rate	18,720		18,850	
pressure product				
(median)				
Angina during test	4	36	29	54
Positive ECG	11	100	10	19
Resting EF (%)	36 $\pm$ 3		39 $\pm$ 1	
Exercise EF (%)	32 $\pm$ 3		38 $\pm$ 2	
Change in EF (%)	-5 $\pm$ 1		-1 $\pm$ 1	
Exercise RWMA	7	64	16	30
Coronary angiography§				
1-vessel disease	3	27	30	56
2-vessel disease	8	73	24	44

* The only significant difference between the 2 groups occurred with respect to positive ECG and change in ejection fraction, which were the variables used to define an ischemic response.

† Defined by history or blood pressure during medical evaluation $>160/90$ mm Hg.

‡ Defined by history or recent cholesterol or triglyceride value >90 th percentile for sex and age.

§ One vessel disease defined as $\geq 70\%$ narrowing in the internal diameter of the left anterior descending, circumflex or right coronary arteries or their major branches; 2-vessel disease as narrowing in 2 of these coronary distributions.

All $\pm$ data are mean $\pm$ standard error.

Change in EF = exercise EF - rest EF; ECG = electrocardiogram; EF = ejection fraction; NYHA = New York Heart Association; RNA = radionuclide angiogram; RWMA = regional wall motion abnormalities.

acting nitrates (32), β blockers (28) and calcium antagonists (14). Fourteen patients were taking digitalis. Sixteen patients were in New York Heart Association functional class III and 15 patients in functional class IV.

Definition of severe exercise-induced ischemia: An exercise radionuclide angiogram was considered ischemic if all of the following were present: a decrease in LV ejection fraction between rest and peak exercise; ≥ 1.0 mm of ST-segment depression on the exercise electrocardiogram (if ST-segment changes were present at rest, an additional 1.0 mm of ST-segment depression was required) and peak exercise workload ≤ 600 kg-m/min. These criteria were selected based on a previous study by Bonow et al,¹⁰ showing that these 3 exercise variables could identify a subgroup of patients with minimal symptoms, 3-vessel CAD and preserved LV function who were at high risk of death during subsequent medical therapy. This definition of an ischemic exercise radionuclide angiogram was chosen for the current study without any knowledge of clinical, angiographic or follow-up data in these patients.

Exercise protocol: Supine bicycle ergometry was performed in 3-minute stages using a previously reported protocol.¹³ Exercise endpoints consisted of marked fatigue, moderate angina, ST-segment depression ≥ 2.0 mm, significant arrhythmias or significant decrease in systolic blood pressure.

Radionuclide angiography: Using either the in vivo¹⁴ or modified in vivo procedure of Callahan et al,¹⁵ each patient's red blood cells were labeled with 30 mCi of technetium-99m. Images were acquired and processed for the determination of ejection fraction using previously reported techniques.¹³

Regional wall motion was subjectively assessed as the consensus of 2 experienced observers.¹⁶ An exercise wall motion abnormality was defined as worsening wall motion in any segment between the rest and exercise studies.

Coronary angiography: Selective coronary angiograms were interpreted using criteria from the Coronary Artery Surgery Study.¹² Significant obstruction was defined as $\geq 50\%$ reduction in internal diameter of the left main coronary artery or $\geq 70\%$ reduction in the diameter of the left anterior descending, circumflex or right coronary arteries or their major branches.¹²

Follow-up procedures: All patients or their physicians were contacted by mailed questionnaire or telephone within a 3-month period. Significant cardiac events were defined as cardiac death, cardiac arrest, myocardial infarction and bypass surgery or angioplasty ≥ 3 months after exercise testing. Follow-up was 100% complete with a median duration in those alive at follow-up of 24 months (range 12 to 49).

Statistical analysis: Event-free survival was estimated using the Kaplan-Meier method.¹⁷ For the purpose of determining event-free survival, patients were censored once they had their first cardiac event. The log-rank statistic¹⁸ was used to assess the statistical significance of the observed differences between survival curves. Cox stepwise proportional-hazards regression analyses¹⁹ were used to determine if any of several variables was associated with the time from the exercise study to a significant cardiac event and death from any cause. The variable severely ischemic exercise radionuclide angiogram was compared to other variables that have previously been shown to be independent prognostic indicators, including age, sex, number of diseased vessels, resting ejection fraction, exercise ejection fraction and peak ST-segment depression.

RESULTS

Exercise test results: Eleven of the 65 patients (17%) had severely ischemic exercise radionuclide angiograms. The data on clinical characteristics, exercise test variables and coronary anatomy are summarized for these 11 patients and the remaining 54 patients in Table I. The only significant difference between the groups occurred with respect to positive electrocardiogram and the change in ejection fraction, which were the variables used to define an ischemic response.

Follow-up data: During follow-up 11 patients had initial major cardiac events, including 4 cardiac deaths,

1 cardiac arrest, 4 myocardial infarctions and 2 late bypass grafting or angioplasty procedures. (One patient who had a myocardial infarction, and therefore was censored at that point from the event-free survival analysis, subsequently had a cardiac death, yielding a total of 5 cardiac deaths.) Both patients who underwent late revascularization were hospitalized before the procedure for unstable angina (5 and 13 months after the exercise radionuclide angiogram). Four of 11 patients (36%) with severe ischemia during exercise testing versus 7 of 54 patients (13%) without ischemia had initial cardiac events. Of the 4 patients with exercise ischemia who had events, 1 had 1-vessel CAD and 3 had 2-vessel CAD. The events in these 4 patients included 1 cardiac death, 1 cardiac arrest, 1 myocardial infarction and 1 revascularization procedure. The event-free survival curves are shown in Figure 1. The presence or absence of severe exercise-induced ischemia was significantly associated with survival free of a cardiac event. Only 73% of patients with severely ischemic radionuclide angiograms were free of events at 18 months follow-up, in contrast to 92% of patients without ischemia ($p < 0.05$). During follow-up 7 of these 65 patients ultimately died, including 2 from noncardiac causes. Overall survival for the entire group decreased to 92% at 3 years.

Cox analysis of significant cardiac events: A Cox stepwise proportional-hazards regression analysis was used to determine which variables were associated with future significant cardiac events (Table II). Severe ischemia on exercise radionuclide angiography was the only variable independently associated with cardiac events on follow-up (chi-square = 8.16, $p < 0.005$). This variable was also significantly associated with "hard" cardiac events (death, myocardial infarction and cardiac arrest) only (chi-square = 4.76, $p < 0.05$). Even after the number of narrowed coronary arteries and resting LV ejection fraction were forced into the Cox model, an ischemic exercise radionuclide angiogram was still an independent, although less powerful, predictor of total events (chi-square = 7.07, $p < 0.01$) but no longer of hard events ($p = 0.08$).

Cox analysis of all-cause mortality: The second Cox regression analysis was performed with death from any cause as the endpoint. The only variables univariately associated with all-cause mortality were the resting ejection fraction (chi-square = 12.72, $p < 0.005$) and exercise ejection fraction (chi-square = 11.71, $p < 0.005$) (Table III). Once resting ejection fraction was entered in the model, the number of narrowed coronary arteries became a significant variable (chi-square = 5.05, $p < 0.05$). When both the resting ejection fraction and number of narrowed coronary arteries were included in the model, no other variables were significant.

DISCUSSION

This study demonstrates that exercise radionuclide angiography can aid in the risk stratification of patients with 1- or 2-vessel CAD and impaired resting LV function. At 18-month follow-up only 73% of the patients with a severely ischemic study were free of significant cardiac events, in contrast to 92% of the patients with-

TABLE II Univariate Analysis for Survival Free of Cardiac Events in 65 Patients

Variable	Chi-Square*	p Value
Severely ischemic exercise RNA	8.16	<0.005
Resting LVEF	<1	NS
Peak exercise LVEF	<1	NS
Male sex	<1	NS
No. of diseased vessels	<1	NS
Age	<1	NS
Peak exercise ST-segment depression	<1	NS

* Univariate chi-square value at the first step in the proportional-hazards regression analysis (values >3.84 imply $p < 0.05$; values >7.88 imply $p < 0.005$). LVEF = left ventricular ejection fraction; NS = not significant; RNA = radionuclide angiogram.

TABLE III Univariate Analysis for All-Cause Mortality for 65 Patients

Variable	Chi-Square*	p Value
Resting LVEF	12.72	<0.005
Peak exercise LVEF	11.71	<0.005
No. diseased vessels	2.50	NS
Severely ischemic exercise RNA	2.05	NS
Male sex	1.29	NS
Age	1.02	NS
Peak exercise ST-segment depression	<1	NS

* As in Table II.
Abbreviations as in Table II.

out an ischemic study (Figure 1). By a Cox proportional-hazards regression analysis, a severely ischemic exercise radionuclide angiogram was the only variable predictive of event-free survival (Table II).

Selection of study criteria: A combination of 3 exercise radionuclide angiographic variables (decrease in LV ejection fraction between rest and peak exercise; ≥ 1.0 mm of ST-segment depression; and exercise work-

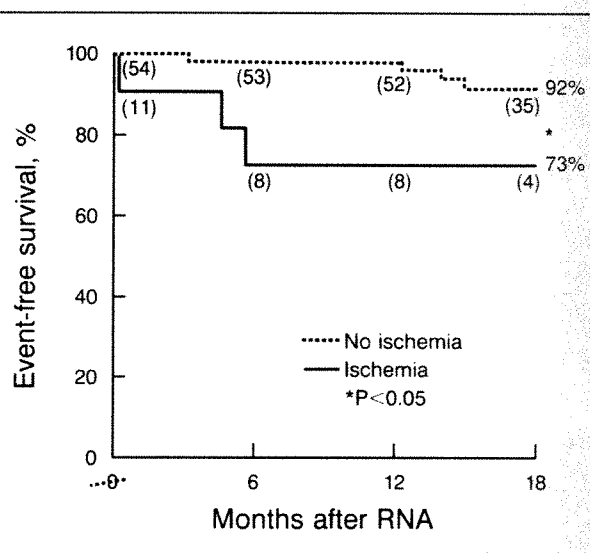


FIGURE 1. Event-free survival curves for patients with (—) and without (---) severely ischemic exercise radionuclide angiograms (RNA). Numbers in parentheses indicate the numbers of patients in each subgroup available for analysis at the specified timepoints.

load ≤ 120 watts) has previously been shown by Bonow et al¹⁰ to identify from among patients with 3-vessel CAD and normal LV function a subgroup at high risk for future cardiac events. The current study was designed to determine if this same combination of 3 variables could identify a high risk subset from among patients with 1- or 2-vessel CAD and impaired resting LV function. We emphasize that these criteria were applied to the current study patients without knowledge of follow-up data. Exercise variables were not simply fitted to the data retrospectively.

We selected late revascularization as an endpoint for our study on the basis of its use in several recently published studies.²⁰⁻²² Although one could always argue that the results of the exercise study influenced the decision to perform revascularization, we felt this was unlikely given these patients' subsequent clinical courses (both hospitalized for unstable angina before revascularization) and the significant delay (5 and 13 months) between the exercise radionuclide angiograms and the revascularization procedures.

Randomized studies and two-vessel coronary artery disease: In contrast to 3-vessel CAD, none of the randomized trials^{5,6,23} reported any overall survival advantage for surgical versus medical therapy in patients with 1- or 2-vessel CAD. The European Study⁶ did, however, show an advantage for 2-vessel CAD only if one of the involved vessels was the proximal left anterior descending coronary artery.

Registry studies and two-vessel coronary artery disease: Registry studies have shown a survival advantage for surgical therapy for some patients with 2-vessel CAD. Hammermeister et al²⁴ reported from the Seattle Heart Watch Registry that surgery improved survival in patients with 2-vessel CAD and moderately impaired LV function (ejection fraction 31 to 50%). The surgically treated patients had more severe angina than the medically treated patients as indicated by a greater mean New York Heart Association functional class. A more recent study by Mock et al²⁵ from the Coronary Artery Surgery Study registry found improved survival for surgical versus medical therapy for patients with 2-vessel CAD, including proximal narrowing of ≥ 1 coronary artery, impaired LV function and functional class III and IV angina on presentation. Thus, although the randomized trials failed to show improved survival for surgical therapy for patients with 2-vessel CAD, registry studies suggest there may be a subgroup with more severe angina and impaired LV function who show benefit, especially if they have involvement of ≥ 1 proximal coronary artery.

Exercise testing for risk stratification in anatomically defined subsets of patients with coronary artery disease: For patients with 3-vessel CAD and preserved LV function, some studies have been able to identify a subgroup at higher risk on the basis of exercise duration and ST-segment depression.⁶⁻⁹ Exercise radionuclide angiography has also been used to aid in risk stratification for this anatomic subset of patients. Bonow et al,¹⁰ as mentioned, found that a combination of exercise variables could identify a subgroup of mildly symptomatic

patients at increased risk of dying during subsequent medical therapy.

The ability of exercise testing to aid in the risk stratification of patients with 1- or 2-vessel CAD has been less well studied. Gohlke et al⁹ divided patients into terciles on the basis of exercise tolerance, angina-free exercise tolerance and maximal heart rate. Patients with 2-vessel CAD and normal LV function had a 15% higher 5-year survival rate if they were in the highest versus the lowest tercile. More recently Mazzotta et al¹¹ reported that exercise ejection fraction and magnitude of change in exercise ejection fraction were significantly associated with future cardiac events (death, heart failure, reinfarction or increased angina requiring surgical intervention) in a group of 53 asymptomatic or mildly symptomatic patients with 1- or 2-vessel CAD and impaired LV function. These 2 variables and the exercise ST-segment response were also significantly associated with mortality. Survival at 6 years was 97% in patients with an exercise ejection fraction $>30\%$ versus 62% if it was $\leq 30\%$, and survival was 100% if the ejection fraction increased during exercise versus 74% if it did not. These findings are similar to those in the current study. Our definition of a severely ischemic radionuclide angiogram incorporated both the change in ejection fraction and exercise ST-segment response, supporting the findings of Mazzotta et al that these variables are predictive of future cardiac events in this subset of patients. Since our patients were more symptomatic (48% in functional class III or IV) than those in the Mazzotta study, we feel our data further strengthen the usefulness of exercise radionuclide angiography by demonstrating that it is beneficial as a prognostic indicator not only for mildly symptomatic patients but also for patients with more severe symptoms.

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Usefulness of Head-Up Tilt Test in Evaluating Patients with Syncope of Unknown Origin and Negative Electrophysiologic Study

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The vasovagal nature of syncope, which remained unexplained despite full clinical and electrophysiologic investigation, was evaluated by means of 60° head-up tilt test for 60 minutes. Thirty patients (17 men and 13 women, mean age 65 years, 19 with and 11 without organic heart disease) with 1 to 28 (mean 5) episodes of syncope of unknown origin were studied. Head-up tilt test was considered positive if syncope developed in association with hypotension, bradycardia, or both. During baseline head-up tilt 15 patients (50%) had a positive response. Ten patients had a vasodepressor response (marked hypotension without marked bradycardia) and 5 had a mixed response (marked hypotension with marked bradycardia). None of 8 control subjects became symptomatic during the test. Baseline head-up tilt test was positively reproducible in 10 of 14 patients (71%). Nine of these 10 patients underwent serial head-up tilt tests after drug administration to determine the pathogenesis of vasovagal syncope. Atropine prevented tilt-induced syncope in 3 of 8 patients (37.5%), propranolol in 2 of 8 (25%) and etilephrine in 7 of 7 (100%). Seven patients received long-term drug treatment with drugs selected on the basis of acute drug testing. One responder to atropine received transdermal scopolamine and 6 received etilephrine. None of these 7 patients had syncopal recurrences or death during a mean follow-up of 12 months. Head-up tilt is a very sensitive and highly specific test to unmask susceptibility to vasovagal reaction in patients with syncope of unknown origin. Withdrawal of α -sympathetic stimulation is a principal mechanism responsible for vasodilation and syncope during head-up tilt. Alpha-sympathomimetic agents, such as etilephrine, are effective in preventing spontaneous episodes of vasovagal syncope during short-term follow-up.

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Syncope is a sudden and transient loss of consciousness that may result from a wide spectrum of cardiovascular, neurologic and metabolic abnormalities.¹ Several studies²⁻⁵ have demonstrated that in most cases (53 to 95%) the cause of syncope can be identified by history, physical examination and a series of laboratory investigations, including an invasive electrophysiologic study. In about 25% of the cases, however, the cause of syncope remains undetermined despite extensive diagnostic work-up.⁶⁻⁸ A vasovagal reaction presenting unusual modalities (for example, absence of typical prodrome) has been advocated as a possible unrecognized cause of syncope in these cases.^{6,7} Prolonged head-up tilt may be of value in reproducing vasovagal syncope in susceptible persons.^{9,10} Thus, recently some investigators have proposed upright tilt test as an aid to detect a propensity to vasovagal reaction in patients with syncope that remained unexplained at the end of an electrophysiologic study.^{6,7,11-13} The present study was undertaken (1) to assess the usefulness of head-up tilt in evaluating syncope of unknown origin, (2) to establish the possible pathophysiologic mechanisms responsible for syncope during the test and (3) to examine the effectiveness of different pharmacologic interventions in preventing induced and spontaneous episodes of vasovagal syncope.

METHODS

Population: Thirty consecutive patients with syncope or presyncope of unknown origin and 8 control subjects were studied.

PATIENTS: Seventeen of the 30 patients were men and 13 were women, with mean age ($\pm$ standard deviation) of 65 ± 14 years (range 14 to 83). Nineteen patients (63%) had organic heart disease and 11 (37%) did not. Thirteen patients had chronic coronary artery disease with previous myocardial infarction in 3 (mean left ventricular ejection fraction $51 \pm 7\%$, range 33 to 60) and 6 had systemic hypertension.

All patients had at least 1 syncopal episode of unknown origin (range 1 to 28, mean 5 ± 6 , median 3) during a period of time ranging from a few days to 54 years (9 ± 13 years, median 1.2 years). Five patients (17%) had only 1 syncopal episode and 25 (83%) had ≥ 2 syncopal or presyncopal episodes.

Syncopal episodes were defined as of unknown origin if no cause was found after the following series of investigations: history, physical examination, orthostatic blood pressure determinations, standard 12-lead electro-

cardiogram, bedside carotid sinus massage, routine laboratory testing, chest x-ray, neurologic evaluation, electroencephalogram, 24-hour Holter monitoring, exercise stress testing, echocardiography and invasive electrophysiologic study including atrial and ventricular programmed stimulation. The protocol used for induction of supraventricular and ventricular arrhythmias consisted of a maximum of 2 extrastimuli during sinus rhythm and during multiple drive cycle lengths (600, 460, 400 and 375 ms). The protocol also included bursts of rapid pacing at progressively shorter cycle lengths until 1:1 capture could no longer be achieved. Ventricular stimulation was performed from 2 right ventricular sites: apex and outflow tract. We did not use a third extrastimulus in our patients because of the great potential for initiation of nonspecific tachyarrhythmias in persons without documented spontaneous arrhythmias.¹⁴

The following clinical, electrocardiographic and electrophysiologic abnormalities were considered definite or potential causes of syncope and served as the criteria of exclusion from the study: typical history of vasovagal syncope¹; postural hypotension (orthostatic decrease of systolic blood pressure >30 mm Hg); carotid sinus hypersensitivity (ventricular pause >3.0 seconds with reproduction of symptoms; ventricular pause >5.0 seconds in absence of symptoms); aortic stenosis; hypertrophic cardiomyopathy; diurnal sinus bradycardia <40 beats/min; nocturnal sinus bradycardia <30 beats/min; sinus arrest or sinus pauses >3.0 seconds; atrial fibrillation with ventricular pauses >3.0 seconds, Mobitz II second-degree atrioventricular block or third-degree atrioventricular block, symptomatic or rapid (heart rate >180 beats/min) supraventricular tachycardia, sustained or unsustained (>10 consecutive beats with rate >180 beats/min) ventricular tachycardia, ventricular fibrillation, torsade de pointes, corrected sinus node recovery time >900 ms, HV interval >70 ms in the control state and >120 ms after ajmaline intravenous administration (1 mg/kg in 1 minute), induction of sustained (>1 minute) and symptomatic atrial flutter or atrial fibrillation or reciprocating supraventricular tachycardia and induction of sustained (>30 seconds) or poorly tolerated ventricular tachycardia or ventricular fibrillation.

CONTROL SUBJECTS: Four of the 8 control subjects were men and 4 were women with mean age of 65 ± 7 years (range 50 to 75). Seven subjects (87%) had organic heart disease and 1 (13%) did not. Five subjects had chronic coronary artery disease without previous myocardial infarction (mean left ventricular ejection fraction $57 \pm 8\%$, range 48 to 69) and 2 systemic hypertension. None ever had episodes of syncope, presyncope, dizziness or any other symptom suggestive of vasovagal reaction.

Head-up tilt test protocol: The head-up tilt test was always performed in the morning (after overnight fasting) between 9:00 A.M. and 12:00 noon to avoid any possible influence of diurnal variation on autonomic tone. The study room was quiet with dimmed lights. All cardioactive and vasoactive drugs were withdrawn for at least 5 half-lives before the study. Informed consent was

obtained from all the patients and control subjects. The tilt table used was an electrically motorized bed with a footboard support and 16 seconds of travel time between 0 and 60°.

The specific head-up tilt test protocol consisted of frequent (every 5 minutes or more often) blood pressure and heart rate measurements (1) during an initial period of supine rest for 10 minutes and (2) during a subsequent period of head-up tilt to 60° for 60 minutes or until symptoms developed. As soon as syncope or presyncope occurred the patient was rapidly returned to the supine position with immediate restoration of consciousness and without any adverse sequel. During the test the blood pressure was measured by cuff sphygmomanometer and the heart rate was measured by continuous electrocardiographic recording. If the head-up tilt was initially positive, patients underwent at least another baseline test on the following days to assess the reproducibility of the test.

Pharmacologic tests: Patients in whom the response during head-up tilt was reproducibly positive in the basal state underwent serial head-up tilt tests after drug administration to identify the pathophysiologic mechanisms underlying syncope induced by tilt. Drugs tested on different days were atropine, propranolol and etilephrine. Atropine sulfate was given intravenously at a dosage of 0.04 mg/kg in 1 minute with the patient in the supine position. Head-up tilt test was then repeated after 5 minutes using the same protocol as in the basal state. Atropine administration served to achieve complete muscarinic blockade¹⁵ and to evaluate the role of an increased vagal tone in triggering vasovagal syncope. Propranolol was given intravenously at a dosage of 0.2 mg/kg in 3 minutes. Five minutes later, the patient was positioned upright and the tilt test repeated. Propranolol, at the dosage used, allowed complete β -adrenergic blockade to be reached,¹⁵ thus allowing the importance of an increased β -sympathetic tone in the pathogenesis of vasovagal syncope to be studied. Etilephrine was given orally at a dosage of 15 to 30 mg/day. Forty-eight to 72 hours after initiation of the therapy, patients were reevaluated and head-up tilt repeated. Etilephrine was used to stimulate α -adrenergic receptors and to assess the role of a reduced or withdrawn α -sympathetic tone in inducing vasovagal syncope.

Patients in whom atropine prevented tilt-induced syncope were given transdermal scopolamine as a transcutaneous patch at a dosage of 1.5 mg for 2 days. Head-up tilt test was then repeated. The purpose was to assess the correspondence of the effect between atropine and scopolamine and the possibility of administering scopolamine for long-term prophylactic therapy.

Definition of terms: Positive response to head-up tilt test was development of syncope or presyncope in association with hypotension, bradycardia or both. Vaso-depressor or predominantly vasodepressor response to head-up tilt test was a decrease in systolic blood pressure to $\geq 60\%$ of supine value without a decrease in heart rate below 45 beats/min at the time syncope occurred. Mixed or vasovagal response to head-up tilt test was a marked decrease both in systolic blood pressure

TABLE I Clinical Characteristics of Patients with Positive and Negative Response to Head-Up Tilt

	Positive Response	Negative Response	p Value
No.	15	15	
Mean age (yrs)	60 ± 16	69 ± 10	NS
Male sex	10	8	NS
Structural heart disease	9	10	NS
Coronary artery disease	4	9	NS
Mean no. of syncopal episodes	7 ± 8	3 ± 2	<0.05
Mean duration of symptoms (yrs)	13 ± 16	5 ± 8	NS
Mean value of supine systolic BP (mm Hg)	149 ± 30	151 ± 20	NS
Mean value of supine HR (beats/min)	66 ± 15	67 ± 14	NS
Mean value of maximal % increase of HR during head-up tilt	22 ± 9	25 ± 11	NS

All ± data are ± standard deviation.
BP = blood pressure; HR = heart rate; NS = not significant; SD = standard deviation.

TABLE II Results of Pharmacologic Tests in Nine Patients with Reproducible Baseline Positive Tests

	Atropine		Propranolol		Etilephrine	
Pts tested	8		8		7	
Type of response to baseline tilt	VD	M	VD	M	VD	M
	6	2	6	2	5	2
Patients in whom drug prevented syncope	3		2		7	
Type of response to baseline tilt	VD	M	VD	M	VD	M
	2	1	2	0	5	2

M = mixed; VD = vasodepressor.

(>60% of supine value) and heart rate (<45 beats/min) simultaneous to or preceding development of symptoms. Drug efficacy during head-up tilt test was prevention of tilt-induced hypotension, bradycardia and symptoms at test repetition after drug administration.

Treatment and follow-up: Patients with frequent recurrent syncopes, if deemed necessary, were treated with drugs on a long-term basis. Prophylactic treatment was always chosen on the basis of the results of pharma-

cologic tests. Patients with mixed response and prolonged sinus arrest or third-degree atrioventricular block during head-up tilt test were also considered candidates for the implant of a dual-chamber pacemaker.

After hospital discharge all treated patients were followed in the outpatient clinic at 3- to 6-month intervals.

Statistical analysis: Statistical analysis was done by using the chi-square test with Yates' correction and the Student *t* test for unpaired observations, as appropriate. A *p* value <0.05 was considered statistically significant.

RESULTS

Baseline head-up tilt test: PATIENTS: The baseline head-up tilt test was positive in 15 of 30 patients (50%). Patients who fainted during the tilt had a significantly higher number of syncopal episodes than patients who did not (Table I). No other variables could predict a positive response. Symptoms during tilt began a mean of 25 minutes (range 2.5 to 56) after the onset of the test.

Ten of the 15 patients (67%) with positive response to tilt showed a vasodepressor or predominantly vasodepressor response (Figure 1) and 5 (33%) a mixed response (Figure 2). The average percent variation in heart rate between supine value and last tilt value was +1% (range -13 to 21) in patients with vasodepressor response and -68% (range -41 to -100) in patients with mixed response. Three of the 5 patients with mixed response had only a sinus bradycardia (between 40 and 45 beats/min) at the time syncope developed while 2 (13%) had a prolonged sinus arrest (10 and 46 seconds, respectively). In all cases, however, onset of hypotension preceded onset of bradycardia. Mean time to syncope after tilt was 25 ± 15 minutes (range 2.5 to 49) in patients with vasodepressor response and 24 ± 20 minutes (range 3 to 56) in patients with mixed response.

The baseline head-up tilt test was repeated in 14 of the 15 patients with initial positive response after a mean period of 3 days (range 1 to 13). One patient did not give consent. The baseline tilt was reproducibly pos-

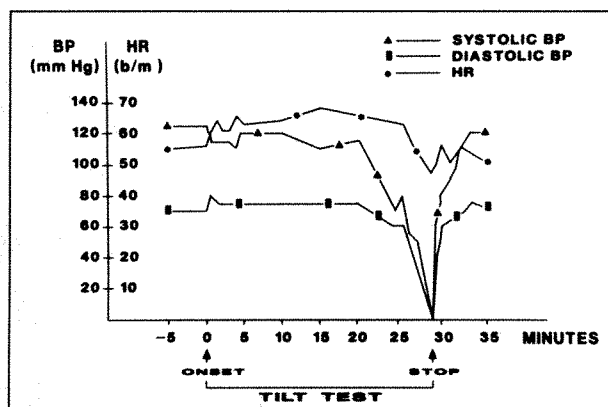


FIGURE 1. Temporal changes in systolic blood pressure (BP), diastolic blood pressure and heart rate (HR) in a patient with a positive response to tilt of vasodepressor type. Syncope developed 29 minutes after tilt and was associated with a marked decrease in blood pressure while heart rate did not significantly decrease.

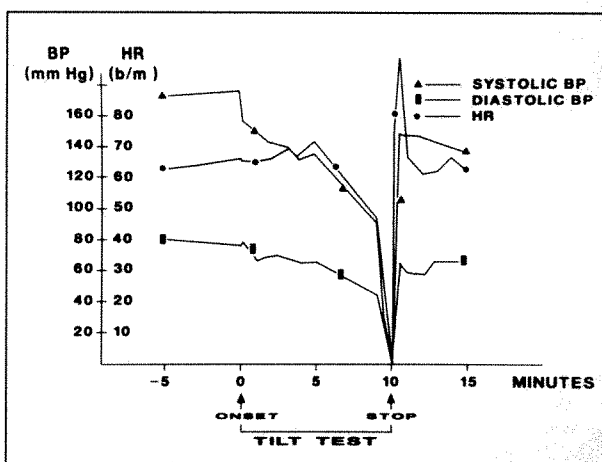


FIGURE 2. Temporal changes in systolic blood pressure (BP), diastolic blood pressure and heart rate (HR) in a patient with a positive response to tilt of mixed type. Syncope developed 10 minutes after tilt and was associated with both marked decrease in blood pressure and heart rate.

TABLE III Previously Published Data on the Results of Head-Up Tilt Test in Patients with Syncope of Unknown Origin and in Control Subjects

Studies	Patients			Control Subjects			Tilt Protocol	
	No.	+ Test	%	No.	+ Test	%	Duration (min)	Angle (°)
Kenny et al ⁶	15	10	67	10	1	10	60	60
Fitzpatrick and Sutton ⁷	71	53	74	27	2	7	45-60	60
Abi-Samra et al ¹²	151	63	42	15	0	0	20-30	60
Almquist et al ¹⁶	15	4	27	18	0	0	10	80
Total	252	130	51.6	70	3	4.3	10-60	60-80

itive in 10 patients (71%). Seven patients showed a concordance in the type of response (vasodepressor or mixed) between first and second test and 3 did not. In particular, 2 patients with mixed response at the initial examination and 1 with vasodepressor response showed a different response at the repetition of the test. The delay between assumption of upright posture and development of syncope was significantly shorter in patients with reproducible response than in patients without (18 ± 13 minutes, range 2.5 to 41, vs 39 ± 10 minutes, range 22 to 49, respectively, $p < 0.005$).

CONTROL SUBJECTS: None of the 8 control subjects had either a positive response to head-up tilt or developed significant hypotension or bradycardia during the test.

Pharmacologic tests: The results of the pharmacologic tests are listed in Table II.

Pharmacologic tests were performed in 9 of the 10 patients in whom the baseline tilt test was reproducibly positive. One patient did not give consent. Not all drugs were tested in every patient. Three patients refused to complete the study protocol after an effective drug had been found. All 3 drugs were tested in 6 cases, both atropine and propranolol in 2 and etilephrine alone in 1. Atropine was tested in 8 cases and was effective in preventing tilt-induced syncope in 3 (37.5%), 2 with vasodepressor and 1 with mixed response. Propranolol was tested in 8 cases and was effective in 2 (25%), both with vasodepressor response. Etilephrine was tested in 7 and was effective in 7 (100%), 5 with vasodepressor and 2 with mixed response. Six patients were responders to only 1 drug (atropine in 1 and etilephrine in 5) while 3 patients were responders to >1 drug (atropine and propranolol in 1, atropine and etilephrine in 1 and propranolol and etilephrine in 1). Atropine was not effective in 5 cases, 1 with mixed response, despite a normal increase in heart rate caused by the drug (105 ± 25 beats/min at the time hypotension and syncope developed vs 72 ± 18 beats/min in the control state).

Scopolamine was tested in 2 of the 3 responders (patients) to atropine and was effective in both.

Follow-up: During the follow-up 7 patients, including the 2 with mixed response and prolonged sinus arrest during baseline head-up tilt, were treated with drugs that were effective during pharmacologic tests. One patient received transdermal scopolamine (Transcop, Ciba-Geigy), 1.5 mg to be changed every other day and 6 patients received oral etilephrine (Effortil, Boehringer-Ingheleim) 15 to 30 mg/day. One of the 2 pa-

tients with pronounced cardioinhibitory response who was prescribed scopolamine also received a dual-chamber pacemaker. The other refused electrical therapy and was only treated with etilephrine. No other patient received pacemaker implantation.

All treated patients experienced several syncopal episodes (11 ± 10 , median 5, range 3 to 28) before the study, with a duration of recurrent syncopes ranging from a few days to 50 years. At least 2 syncopal episodes had occurred within the last 6 months and patients had often injured themselves during the episodes.

The follow-up averaged 12 months (range 9 to 16). During this period no patient had syncopal recurrences except 1 who had discontinued etilephrine 4 months earlier in coincidence with a gastric hemorrhage. No deaths occurred during the follow-up. Side effects from scopolamine included dry mouth and localized eczematous reaction, while etilephrine was generally well tolerated.

DISCUSSION

Recent studies regarding the usefulness of a head-up tilt test in diagnosing vasovagal syncope have reported very promising results (Table III).^{6,7,12,16} On the whole, a positive response has been observed in >50% of the patients with syncope of unknown origin and in only 4.3% of asymptomatic control subjects.

In the present study we further evaluated the role of head-up tilt in unexplained syncope. Several observations can be made on the basis of our results.

Passive upright posture induced symptomatic hypotension associated (or not) with bradycardia in 15 of our 30 patients (50%) with syncope that remained undetermined despite extensive diagnostic work-up and in 0 of our 8 age-matched control subjects. These data confirm those previously reported^{6,7,12,16} and indicate that head-up tilt is a very sensitive and highly specific test. We used (like others^{6,7}) a tilt duration of 60 minutes at 60° and obtained a greater diagnostic yield (50%) than that achieved by Almquist et al¹⁶ and Abi-Samra et al¹² (27 and 42%, respectively), who used upright posture for a shorter time (10 or 20 minutes) to a similar or larger angle (60 to 80°). Our tilt procedure was not associated with a decrease in the specificity of the test. Thus, a protocol with prolonged head-up tilt may be preferable to enhance the sensitivity of the test.

Two-thirds of our patients with positive head-up tilt showed a vasodepressor or predominantly vasodepressor response during the test and one-third a mixed response.

This is in agreement with the data of Abi-Samra et al,¹² who reported that hypotension is always present at the time syncope develops, while bradycardia may or may not be present. Moreover, when the 2 events occur, hypotension almost always precedes bradycardia.^{1,17,18} This indicates that vasodilation is the principal mechanism responsible for hypotension and tilt-induced syncope while bradycardia is generally a later or secondary phenomenon that can only aggravate but not precipitate the symptoms. This is also indirectly confirmed by the constant prevention of syncope (100% of the cases) in our 7 patients in whom vasodilation and hypotension were corrected by etilephrine and by the inconstant prevention of syncope (37.5% of the cases) in the 8 patients in whom bradycardia was corrected by atropine. However, it is important to note that in patients with mixed response, bradycardia can undoubtedly play a role in accentuating hypotension and making the process self-perpetuating. Indeed, Kenny et al⁶ and Fitzpatrick et al^{7,19} have reported that the short- and long-term efficacy of dual-chamber pacing is as high as 52% in patients with vasovagal syncope and an important "cardioinhibitory" component.

The reproducibility of a baseline positive head-up tilt in our patients was 71%. This value is only slightly lower than that (77%) found by Fitzpatrick and Sutton⁷ in their 31 patients. The lack of reproducibility in 29% of our cases with positive response is not surprising because of the sporadic and unpredictable nature of neurally mediated syncopes.¹ We did not repeat tests in patients with baseline negative head-up tilt. It is possible that some of these patients would have shown a positive response if the test had been repeated on the following days. However, patients with negative responses at the initial examination should undergo isoproterenol infusion in conjunction with upright tilt test to further evaluate and unmask susceptibility to vasovagal syncope.^{16,17,20}

In 9 of our 10 patients with reproducible baseline positive head-up tilt, we repeated the test after drug administration. Atropine was given to evaluate the importance of vagal overtone and propranolol and etilephrine to determine an increased β -sympathetic activity or a decreased α -sympathetic stimulation, respectively. All patients became asymptomatic after etilephrine administration and only 37.5% after atropine and 25% after propranolol administration. These results must be interpreted with caution due to the small number of patients studied and the possible day-to-day variability in the individual propensity to vasovagal reaction¹ that may have occurred in our patients despite a reproducible baseline positive test. Nevertheless, the pharmacologic tests we performed confirm the prominent role of vasodilation in inducing neurally mediated syncope, as already suggested by the different time course of hypotension and bradycardia.^{1,12,18,20}

Furthermore, our results indicate that the most important factor in determining arteriolar vasodilation is withdrawal of α -adrenergic stimulation, as clearly demonstrated by the constant efficacy of etilephrine in our cases and as already shown by Almquist et al²¹ for the

vasodepressor component of carotid sinus hypersensitivity. However, it is not possible to exclude that a reflex discharge of cholinergic sympathetic vasodilator fibers may play in some cases an important role in causing or aggravating tilt-induced vasodilation,²²⁻²⁴ because of the efficacy of atropine in 3 of our patients, 2 of whom had vasodepressor or predominantly vasodepressor response. Finally, although rare, an increased β_2 -adrenergic activity could be responsible for the arteriolar vasodilation leading to syncope. Indeed, propranolol was effective in 2 of our patients with vasodepressor response, similar to the observations made by Goldenberg et al²⁵ for metoprolol in 9 patients with neurally mediated syncope evaluated with head-up tilt. However, the beneficial effects of a β -blocking agent could also be due to the negative cardiac inotropic action of this drug^{20,26,27} with resultant decrease in ventricular wall tension, reduced stimulation of cardiac sensory receptors with vagal afferents²⁸⁻³⁰ and prevention of the so-called "ventricular syncope."²⁴

Our follow-up data (regarding patients chronically treated with the drugs that were most effective in preventing tilt-induced syncope) suggest that head-up tilt may be used to choose prophylactic therapy in patients with recurrent vasovagal syncopes. Indeed, none of our 7 patients (1 treated with scopolamine and 6 with etilephrine) experienced syncopal recurrences during a mean follow-up of 12 months, except 1 who had a new syncopal episode after having stopped etilephrine 4 months earlier. Our follow-up data also suggest that α -sympathetic agents such as etilephrine may be of value and relatively well tolerated in preventing spontaneous neurally mediated syncopes. Similar results have been reported already by Almquist et al²¹ in 8 patients with carotid sinus hypersensitivity and pronounced vasodepressor response in whom syncopal episodes could be prevented by another α -adrenergic agonist, ephedrine, during a follow-up period of 5 to 18 months.

Our findings, despite the limited number of patients studied, the problems in evaluating transient and unpredictable events such as vasovagal reactions and the short duration of follow-up, raise 5 clinically relevant issues. (1) Head-up tilt test is a useful tool for evaluating syncope of unknown origin. (2) Syncopes that remain undetermined despite full clinical and electrophysiologic evaluation are due to a vasovagal reaction in about 50% of the cases. (3) Hypotension induced by tilt is probably caused by a paradoxical reflex vasodilation while the cardioinhibition, when present, is generally a later or secondary phenomenon, or both. (4) Lack of α -sympathetic stimulation seems to be an important mechanism for vasodilation and syncope during head-up tilt; vagal overactivity and increased β -sympathetic tone, however, may play an additional role in some cases. (5) Alpha-sympathetic agents, such as etilephrine, are very effective and relatively well-tolerated drugs in preventing spontaneous episodes of neurally mediated syncope, at least during a short-term follow-up.

Obviously, these conclusions are preliminary and need to be confirmed by further studies in a larger number of patients and over a longer period of time.

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Effectiveness of Propranolol Added to a Type I Antiarrhythmic Agent for Sustained Ventricular Tachycardia Secondary to Coronary Artery Disease

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The effect of adding propranolol to procainamide, quinidine, propafenone or disopyramide was prospectively evaluated in 37 patients, all with prior infarction and inducible ventricular tachycardia (VT). After showing that VT remained inducible during therapy with a type I drug, 23 patients received intravenous propranolol. The ventricular effective refractory period, prolonged by the type I agent, was further increased by propranolol. The cycle length of the VT also increased after the type I drug and propranolol exaggerated this effect. Seven of the 23 patients were rendered non-inducible after propranolol and another 10 manifested a >100 ms increase in induced VT cycle length. In the other 14 patients, propranolol was infused immediately after the basal study. If VT remained inducible, testing was repeated after a type I drug was added. The ventricular effective refractory period, as well as the VT cycle length, increased after propranolol and was further prolonged after the addition of a type I agent. Seven of these 14 patients were rendered noninducible, 3 with propranolol alone and 4 others with the combination, and in 4, the VT cycle length was prolonged by >100 ms. A total of 17 patients were discharged on either propranolol alone (3 patients) or on an effective combination (14 patients). During a mean follow-up of 20 months, 1 patient died suddenly, 2 had recurrence of well-tolerated VT and 9 remain on therapy. Thus, propranolol has a demonstrable antiarrhythmic effect in the invasive laboratory and may supplement the antiarrhythmic efficacy of conventional type I antiarrhythmic drugs.

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Beta-adrenergic blockade protects patients against sudden death after a myocardial infarction.^{1,2} The mechanism for this protection has not been determined, but may be due to a number of cardiac effects of β blockade. Among these is diminished vulnerability to ventricular fibrillation demonstrable in the basic laboratory as an increase in the threshold current required to induce that arrhythmia.³ In addition, blockade of catecholamine effect at the β receptor might be expected to have a favorable effect on electrophysiologic properties that predispose to a malignant arrhythmia.⁴ It would even appear that β stimulation may reverse the beneficial effects of conventional antiarrhythmic agents.^{5,6}

It was with these facts in mind that we embarked on a prospective evaluation of the effect of β blockade on inducible, sustained ventricular arrhythmias. We incorporated a protocol in which the electrophysiologic effects of β -adrenergic blockers could be determined with and without conventional antiarrhythmic agents. We also conducted a follow-up survey to ascertain the symptom status and survival of patients so treated.

METHODS

Consenting patients referred to the cardiac arrhythmia service at the Medical College of Pennsylvania were eligible for inclusion in the study. All patients had had a history of sustained ventricular tachycardia (VT) (lasting >30 seconds or requiring intervention for termination) or ventricular fibrillation outside the setting of an acute myocardial infarction. Patients who had recent or uncontrolled congestive heart failure, active ischemic heart disease or a very low ejection fraction (<15%) were excluded. Also excluded were those who had any contraindication to the use of a nonselective β -blocking agent, such as severe peripheral vascular disease or bronchospastic lung disease.

In each patient, a standard baseline electrophysiologic test was carried out. The programmed stimulation protocol has been described in previous studies.⁷ The ventricular effective refractory period was measured using a single 2.0 ms extrastimulus set at twice the pacing threshold and introduced after 8 paced beats (500 ms drive). The effective refractory period was defined as the longest S₁S₂ interval that did not generate a V₂. Ventricular tachycardia was induced using 1 to 3 sequential extrastimuli introduced decrementally at up to 2 right ventricular sites using 2 drive cycle lengths of

500 and 400 ms. When a sustained monomorphic VT was induced, it was terminated either by pacing or external cardioversion and then reproduced after a 15-minute wait before any drug administration.

Patients were assigned to 1 of 2 groups. In group 1, a type I antiarrhythmic drug was administered either intravenously or orally. Oral doses were titrated to a therapeutic blood level, or to a target electrocardiographic conduction interval increase (20 to 25% increase in PR, QRS or QT interval). At steady state, the programmed stimulation study was repeated. Those patients who remained inducible to sustained VT then received 0.15 mg/kg of intravenous propranolol and testing was repeated. Group 2 patients received intravenous propranolol as initial therapy and were restudied. If they remained inducible, they received an intravenous type I drug (either procainamide or quinidine) before restudy. The doses used for intravenous administration were 15 mg/kg of procainamide followed by an infusion of 2 mg/min or quinidine 10 mg/kg infused over 30 to 60 minutes.

Treatment success was defined as inability to induce VT or induction of a VT which had a cycle length ≥ 100 ms $>$ baseline and did not cause hemodynamic deterioration. These patients were eligible for discharge on the successful program, at the investigator's discretion.

Results are expressed in all figures as the mean $\pm$ standard deviation. Results were compared using Student's *t* test and were considered significantly different if *p* was <0.05 .

RESULTS

A total of 37 patients participated in the study (28 men, 9 women, aged 46 to 78 years, mean 61). All had

had a myocardial infarction from 2 to 58 months (mean 18) before they were studied. The average left ventricular ejection fraction for the entire group was $38 \pm 4\%$.

The type I antiarrhythmic drugs used in the study were intravenous procainamide (14), intravenous quinidine (11), oral propafenone (6) and oral disopyramide (3). In 3 others, only propranolol was used.

Group 1: Twenty-three patients received a type I antiarrhythmic drug as initial therapy. The ventricular effective refractory periods and VT cycle lengths for each patient and the mean and standard deviations are shown in Figures 1 and 2. As expected, the type I drug increased the effective refractory period and VT cycle length. Propranolol increased the sinus cycle length from 838 ± 42 to 968 ± 44 ms ($p < 0.05$). In addition, the combination of type I drug and propranolol rendered 5 patients noninducible. Six others had an increase in ventricular cycle lengths >100 ms compared to baseline. In the group as a whole, propranolol caused an increase both in the ventricular effective refractory period and VT cycle length, although the changes were not statistically significant for either parameter.

Group 2: Fourteen patients received intravenous propranolol before treatment with a type I drug. The effects of propranolol alone and the combination on effective refractory period and VT cycle length are shown in Figures 3 and 4. Propranolol alone rendered 3 patients noninducible; another 4 could not be induced to sustained VT after the addition of a type I drug. An additional 4 patients had satisfactory rate slowing after the combination was administered. Overall, propranolol increased sinus cycle length from 809 ± 62 to $1,000 \pm 49$ ms ($p < 0.03$) and increased both effective refractory period and VT cycle length, although the magnitude of

FIGURE 1. Ventricular tachycardia cycle length in milliseconds for group 1 patients studied at baseline, after type I antiarrhythmic drug and after the combination. Seven dashed lines indicate those patients who were noninducible after the combination. Bars in this and succeeding figures represent means and standard deviations for each intervention. NS = not significant.

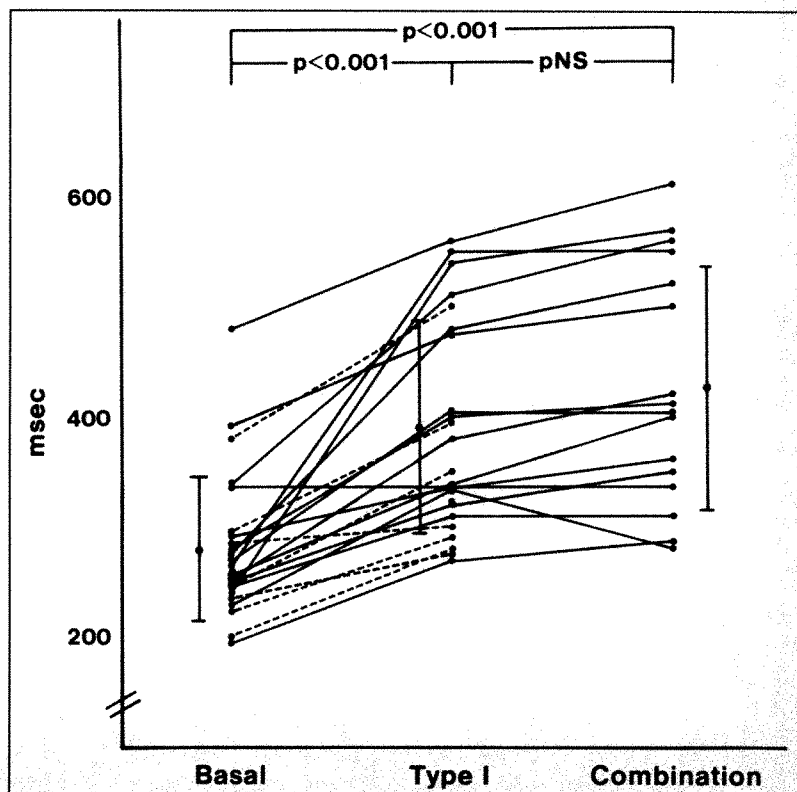


TABLE I Summary of Clinical Results

	Group	
	1	2
No. patients	23	14
No improvement	6	3
Improvement	17	11
Noninducible	7	7
Increase VT CL >100 ms	10	4
Discharged on combination	11	6
Follow-up (20 months)		
Sudden cardiac death	1	0
VT recurrence	1	1
Noncardiac death	2	0
Intolerant	1	2
On therapy	6	3

CL = cycle length; VT = ventricular tachycardia.

these changes was less than that seen with the addition of a type I drug.

Long-term follow-up: Table I lists the testing results and follow-up information. Twenty-eight of the 37 patients achieved a result that was sufficient to consider discharge on that program. The mean left ventricular ejection fraction in the 28 responders was not significantly different compared to the other 9 (37 ± 2 vs $41 \pm 5\%$; difference not significant). Of these, 14 were actually discharged on an oral type I/ β blocker combination and 3 on β blocker alone. The type I drugs used long-term included procainamide (6), quinidine (4), propafenone (3) and disopyramide (1). The dose of oral drug was selected and titrated to a target blood level or pharmacodynamic effect, which in the case of β blocker was a blunted heart rate response (<30% increase) dur-

ing exercise. During a 20-month mean follow-up, there has been 1 sudden death, 2 recurrences of well-tolerated VT, 2 noncardiac deaths and 3 discontinuations due to intolerance. The other 9 patients remain on their combination and are alive and well.

DISCUSSION

Beta-adrenergic blockade is highly effective treatment for the management of a wide variety of cardiac rhythm disturbances, including ventricular arrhythmia.⁸ In fact, 2 agents, propranolol and acebutalol, have been reviewed by the Food and Drug Administration and have been approved for that indication.⁹ Previous studies have documented the efficacy of β blockade as solitary therapy for nonreentrant VT, even when sustained and life-threatening.^{10,11} Despite this track record, it has been the observation of clinical electrophysiologists that when used alone, β blockers are not particularly protective against sustained ventricular arrhythmias that are induced in the electrophysiology laboratory and are re-entrant in nature.¹² However, there has been a strong suggestion that β blockers may be useful as adjunctive therapy in patients treated, but not completely effectively, with conventional antiarrhythmic agents.¹³

Our study examined this issue in more depth in the electrophysiology laboratory. To determine the effects of each class of agent used, the study was performed in 2 stages. We observed a supplemental effect of adding a β blocker to a type I drug. Both refractory period and VT cycle length were prolonged to a greater extent with the combination over and above that seen with the membrane-stabilizing drug alone. These effects might account for the augmented efficacy of the combination seen in this and other studies. They are also in line with

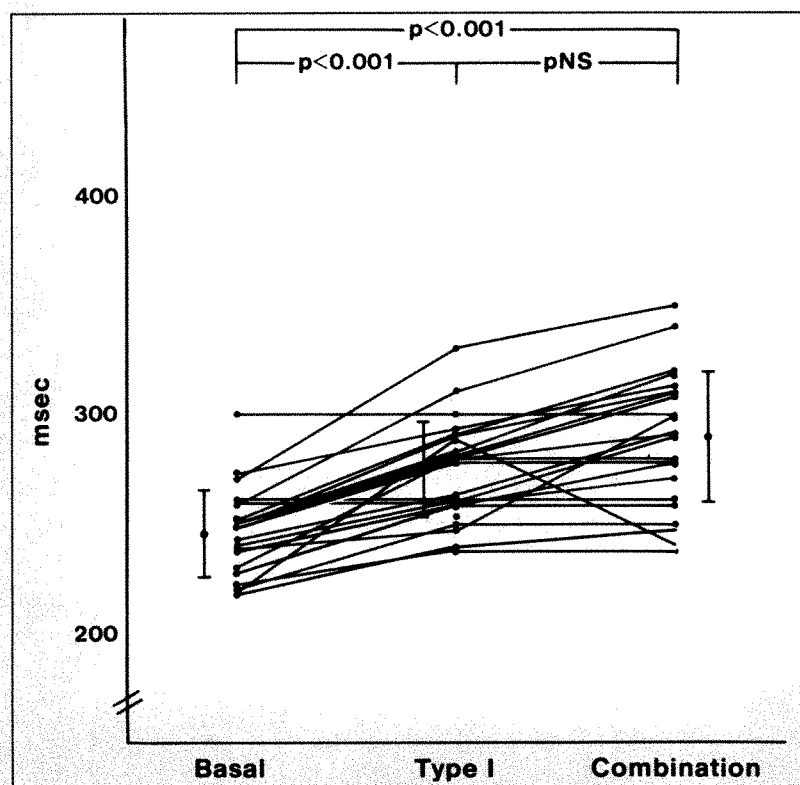


FIGURE 2. Effective refractory period in milliseconds for group 1 patients studied at baseline after type I antiarrhythmic drug and after the combination. Abbreviations as in Figure 1.

previously published data that have proven that catecholamine infusions reverse the beneficial electrophysiologic effects of type I drugs.^{5,6} Like Duff et al,¹⁴ we also found that β blockers alone may render a percentage of

this relatively select group of patients noninducible. This is intriguing since nearly all of our patients had previous infarction and VT was induced with programmed stimulation, suggesting a reentrant mechanism. Huikuri et

FIGURE 3. Ventricular tachycardia cycle length in milliseconds for group 2 patients studied at baseline, after propranolol alone and with the combination. *Circled points* represent 3 patients rendered noninducible on propranolol alone. *Four dashed lines* indicate 4 patients who were non-inducible on the combination. Abbreviation as in Figure 1.

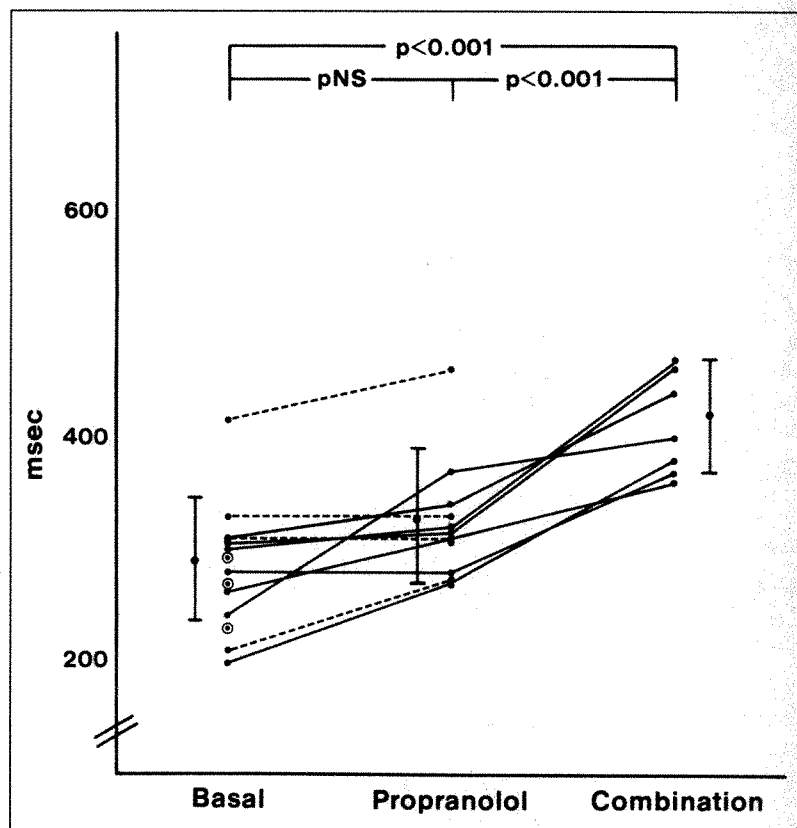
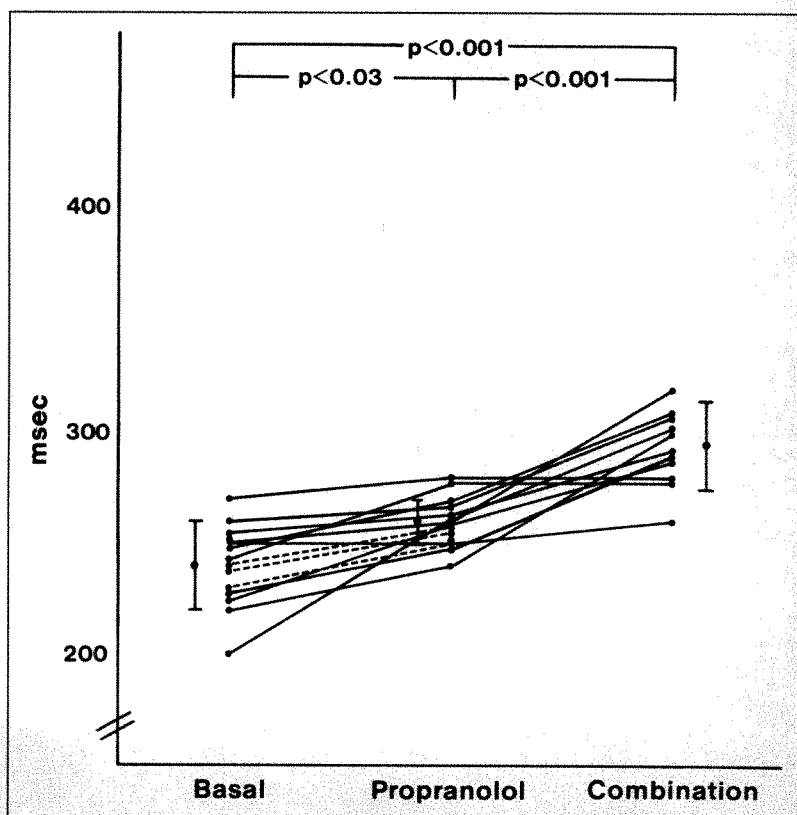


FIGURE 4. Effective refractory period in milliseconds for group 2 patients studied at baseline, after propranolol alone and with the combination. *Three dashed lines* indicate those cases on which propranolol alone rendered the patient noninducible.



al¹⁵ recently reported a similar efficacy in patients with coronary artery disease, although they found a substantially greater benefit in fast, polymorphic VTs compared to monomorphic VTs with slower rates.

The mechanism for the supplemental protection afforded by propranolol in this study is unclear. A direct membrane-stabilizing effect is unlikely, given the doses of propranolol used.¹⁴ It is more likely that β blockade prevents catecholamine-associated shortening in refractoriness and conduction velocity. This effect may be magnified in the electrophysiology laboratory, where the stress of undergoing an invasive study and having a malignant arrhythmia induced repetitively might be expected to lead to an exaggerated catecholamine response.¹⁶ Why so few of our patients had recurrence of sustained VT or sudden death is also unclear. Beta blockers have a dramatic effect on ventricular vulnerability and have been shown to improve survival in patients after myocardial infarction.^{2,17} Whether the same mechanism of cardioprotection was operative in this study is an interesting hypothesis. Unfortunately, our study had an inadequate number of patients to draw any real conclusions about survival.

Our study has limitations. Although each patient was carefully studied, our cohort consisted of only a small number of patients, increasing the chances of a statistical error. Antiarrhythmic drugs were not randomly assigned. Physicians were permitted to use 1 of 4 different type I agents based on evidence of prior inefficacy or intolerance. In addition, we excluded patients at risk from the negative inotropic effects of β blockade, especially those with a history of congestive heart failure. Paradoxically, as shown in subgroup analyses of the postmyocardial infarction trials, those individuals with the very worst left ventricular function may be the ones who derive the most benefit from β blockade, including those with a history of congestive heart failure.^{18,19} Although we found a low frequency of adverse effects in this study, even with long-term therapy, we recommend careful patient selection and supervision, especially when patients are already receiving negative inotropic antiarrhythmic drugs, such as disopyramide, flecainide, or propafenone. In addition, response to antiarrhythmic drugs may be influenced by this selection bias. Patients with good left ventricular function have been found to respond to drug therapy, selected on the basis of invasive or noninvasive testing, with a greater frequency than those with more impaired ventricles.^{20,21} This might explain our relatively high noninducibility rate even with β blocker alone.

We did not systematically design the testing of oral β blocker programs. In fact, the doses of oral β blocker were an approximation of what might be needed based on the heart rate response in the electrophysiology laboratory. This renders the interpretation of our long-term experience suspect even though some of our patients were studied later on oral propranolol. In these cases, results were concordant and not presented here. A prospective study of carefully adjusted oral doses is necessary for this purpose.

We used a variety of type I drugs in this study. There is some reason to believe that some combinations

may be better than others. On theoretical grounds, β blockers might be expected to augment the effects of type IA drugs more than type IC agents since the former prolong the plateau phase of the action potential in addition to reducing the slope of phase 0. We did not observe such a differential effect although the number of patients exposed to each agent was insufficient to make these distinctions. To resolve this very important issue would require a study in which only a single agent from each of these classes would be used alone and then in combination with β blocker, and direct comparisons made, optimally in the same patients.

We did not include data regarding the combination of a class III agent and β blocker. Beta blockers have been used with good success in combination with amiodarone as reported by Tonet et al.²² Sotalol, a drug that combines class III effect with β blockade, may have superior efficacy in rendering sustained VT noninducible in the electrophysiology laboratory.²³

Only 1 intravenous β blocker was used in this trial. Propranolol is a nonselective β blocker that does have membrane stabilizing activity at high doses.²⁴ Whether the results can be extrapolated to other β blocking agents or not is unknown and it would require a separate study to make that determination.

Finally, we combined the endpoints of noninducibility and prolongation of VT cycle length and characterized both as satisfactory. This remains a controversial point since some investigators have shown a higher recurrence rate despite better survival in patients whose VT is slowed to hemodynamic tolerance.²⁵ The number of patients followed long-term in this study is inadequate to carry out a detailed analysis of our results along these lines.

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Changes in Regional Adrenergic Tone During Sustained Ventricular Tachycardia Associated with Coronary Artery Disease or Idiopathic Dilated Cardiomyopathy

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The hemodynamic tolerance of an episode of ventricular tachycardia (VT) can vary widely from no decrease in systolic blood pressure to severe hypotension. Little is known about the factors responsible for these different responses in man. Previous animal studies have suggested an important role for vasoconstriction mediated by the α -adrenergic nervous system. To determine the magnitude and time course of changes in α -adrenergic tone during symptomatic sustained monomorphic VT, VT cycle length, mean and phasic arterial pressure, forearm blood flow (by venous occlusion plethysmography) and forearm vascular resistance were measured in 15 patients. Nine of these patients were studied before and after regional intraarterial α blockade with phentolamine. After the induction of VT (350 ± 68 ms), mean forearm blood flow decreased from 3.2 ± 1.1 to 2.2 ± 0.8 ml/min/100 ml ($p = 0.0002$) and the forearm vascular resistance increased from 32 ± 14 to 40 ± 14 units ($p = 0.01$). There were no significant differences for forearm vascular resistance during the first and last 30 seconds of VT (41.3 ± 14 vs 37 ± 13 units). After the infusion of intraarterial phentolamine, there were no significant changes in the VT cycle length or mean arterial pressure, but the forearm vascular resistance increase during VT was blunted by 60 to 70%.

Most patients with symptomatic VT demonstrate sympathetic vasoconstriction and these changes are maximal during the first 30 seconds of VT. This sympathoexcitatory response is due largely to stimulation of α -adrenoreceptors and may be mediated by arterial baroreflexes.

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The autonomic nervous system plays an important role in the genesis of ventricular arrhythmias.¹⁻⁴ Hemodynamic tolerance and clinical symptomatology during an episode of ventricular tachycardia (VT) vary widely from minimal symptoms to syncope resulting from severe hypotension. Little is known about the different factors responsible for these varying responses. The baroreflexes mediate vasoconstrictor responses during hypotension, and may play an important role in the modulation of the severity of hypotension during VT.

Our understanding of the autonomic changes that occur during induced ventricular arrhythmias is based primarily on animal studies.^{5,6} These studies demonstrate increases in cardiac and peripheral sympathetic nerve traffic as well as elevated plasma catecholamine levels after single premature ventricular complexes and couplets.⁷⁻⁹ The increase in sympathetic nerve traffic after premature ventricular complexes is believed to be mediated largely by arterial baroreflexes. There is, however, little information about changes in sympathetic outflow during *sustained* ventricular arrhythmias in humans.

Venous occlusion plethysmography is a noninvasive technique for measurement of changes in forearm blood flow and calculation of changes in forearm vascular resistance. This measurement is an approximation of regional changes in sympathetic outflow to a vascular bed and can detect rapid changes in sympathetic tone. We measured the magnitude and time course of changes in forearm vascular resistance during sustained monomorphic VT, before and after α blockade.

METHODS

The study group consisted of 15 patients referred for evaluation of symptomatic VT due to coronary artery disease or idiopathic dilated cardiomyopathy. All patients underwent angiography with left ventriculography to determine ejection fraction. No patient had symptoms of New York Heart Association class IV congestive heart failure. Patients with diabetes mellitus or inability to cooperate with the measurement of forearm blood flow because of other systemic diseases (e.g., Parkinson's disease) or previous trauma to the arm or brachial arteries were also excluded from this study. All calcium antagonists, β blockers, angiotensin converting

enzyme inhibitors and nitrates were withheld for at least 4 half-lives before the study. Diuretics were discontinued at least 24 hours before.

All studies were performed in fasting, nonsedated patients after they gave written, informed consent. The protocol was approved by the institutional review boards of The Medical College of Virginia and the McGuire Veterans Affairs Medical Center. Two or 3 multipolar catheters were introduced percutaneously through the femoral vein and positioned in the heart in the right atrial appendage, His bundle and right ventricular apex under fluoroscopic guidance. An 18-gauge, Teflon-coated cannula was inserted into the right brachial artery for continuous arterial pressure monitoring and infusion of phentolamine. All forearm blood flow measurements were taken from the same arm into which phentolamine was infused.

Programmed electrical stimulation was performed with a custom designed, programmable stimulator (Bloom Associates) and recordings were made with a 16-channel physiologic recorder (VR-16, Electronics for Medicine) at a paper speed of 50 to 100 mm/s. Pacing was performed at a pulse width of 2 ms and an amplitude twice diastolic threshold throughout the study. Programmed electrical stimulation was performed from the right ventricular apex and right ventricular outflow tract at 2 (600 and 400 ms) or 3 (600, 500 and 400 ms) cycle lengths with up to 3 extrastimuli.

Venous occlusion plethysmography: Forearm blood flow was measured by venous occlusion plethysmography with a mercury-in-silastic strain gauge plethysmograph (EC-3 or EC-4; D.E. Hokanson). We used a technique of venous occlusion plethysmography previously described in detail.¹⁰ The strain gauge was placed approximately 5 cm below the antecubital crease of the right arm. The arm was elevated so that the proximal

part of the forearm was 10 cm above the anterior chest wall. The pressure of the venous occlusion or congesting cuff on the arm was 40 to 50 mm Hg. Circulation to the hand was arrested by inflating a cuff around the wrist to suprasystolic pressures during determination of forearm blood flow. A minimum of 5 consecutive curves was averaged to obtain a mean value. Forearm blood flow and phasic or mean arterial pressure were recorded on a strip chart recorder (Gould 2800S). Forearm vascular resistance was calculated by dividing the mean arterial pressure (diastolic plus one-third of pulse pressure, in mm Hg) by the forearm blood flow (expressed as ml/min/100 ml of forearm volume). Forearm vascular resistance values are expressed as units throughout.

Study protocol: After completion of the clinically indicated electrophysiology study, the patient rested comfortably in the supine position for 15 to 20 minutes. Baseline heart rate, mean and phasic arterial pressure and forearm blood flow were measured. Programmed electrical stimulation was then repeated using coupling intervals similar to those previously used to induce sustained (monomorphic) VT. During induction of VT, cycle length, mean and phasic arterial pressure and forearm blood flow were measured. Forearm blood flow was measured constantly during the first 3 minutes of VT, which was then terminated by overdrive burst pacing or extrastimuli.

In 9 patients, 3 mg of phentolamine was infused in the right brachial artery over 10 minutes with a Harvard infusion pump. After a stable baseline was reestablished, VT was reinduced. Arterial pressure, VT cycle length and forearm blood flow were measured again. Adequacy of α -adrenergic blockade was assessed by measuring forearm blood flow immediately after phentolamine infusion and after a 50 μ g intraarterial bolus of phenylephrine ($n = 5$).

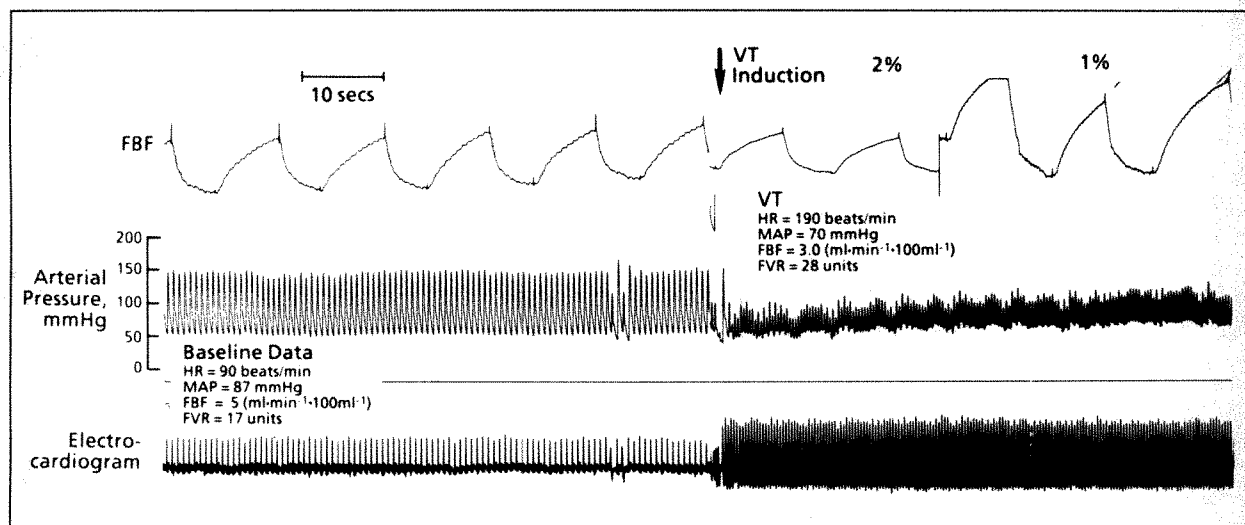


FIGURE 1. Analog data from a patient showing the recording of simultaneous surface electrocardiogram, phasic arterial pressure (mm Hg) and forearm blood flow (FBF, ml/min/100 ml) at baseline and after the induction of sustained ventricular tachycardia (VT). Time scale for electrocardiogram, arterial pressure and FBF are the same. The 2% and 1% above FBF curves refer to the sensitivity scale of the flow measurements (e.g., 2% is more sensitive than 1%). A less sensitive setting was used because of the marked vasoconstriction during VT measured in this patient. HR = heart rate; MAP = mean arterial pressure; FVR = forearm vascular resistance.

Statistics: The data were organized to perform 3 general analyses. First, the effect of VT was analyzed by determining changes from baseline. Second, the effect of phentolamine was analyzed by comparing changes before and after phentolamine. Third, the responses during the first 30 seconds of VT were compared to the last 30 seconds of VT to determine the time course of responses during VT. A paired *t* test was used to perform these comparisons. Multiple comparisons to baseline were corrected using the Bonferroni adjustment. A *p* value <0.05 was accepted as statistically significant. Spearman correlation coefficients were obtained to determine which variables correlated with the change in forearm vascular resistance before and after phentolamine.

RESULTS

The mean age of the patient population was 63 ± 9 years (range 46 to 76). Twelve patients had underlying coronary artery disease with a previous myocardial infarction (inferior in 9, anterior in 3) and 3 patients had dilated cardiomyopathy. Eight patients had symptoms of New York Heart Association class II congestive heart failure and 7 patients had symptoms of class III congestive heart failure. The mean ejection fraction was $38 \pm 9\%$ (range 28 to 55).

The mean VT cycle length was 350 ± 21 ms (range 290 to 410). Ten episodes of VT were characterized by a right and 5 by a left bundle branch morphology.

The baseline mean arterial pressure was 91 mm Hg (range 70 to 130) and decreased by 14 ± 5.0 mm Hg during sustained VT ($p = 0.01$ vs baseline). The systolic arterial pressure decreased by 33 ± 6 mm Hg ($p = 0.0002$ vs baseline) during VT.

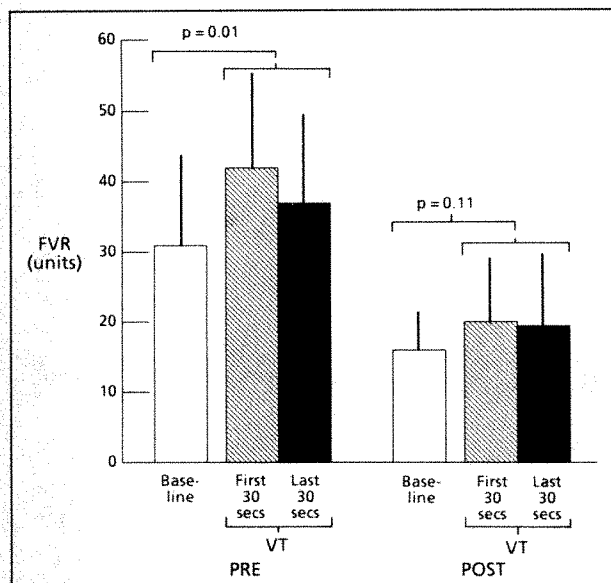


FIGURE 2. Group mean values ($\pm$ standard error of the mean) of forearm vascular resistance (FVR) during the first and last 30 seconds of sustained ventricular tachycardia (VT); before (PRE) and after (POST) infusion of intraarterial phentolamine. In 4 patients, values for forearm blood flow and FVR could not be calculated during the first or last 30 seconds.

Regional blood flow: Sample curves of forearm blood flow during sinus rhythm and VT are shown in Figure 1. The mean forearm blood flow was 3.2 ± 1.1 ml/min/100 ml at baseline; the mean forearm vascular resistance was 32 ± 14 units at baseline. After the induction of sustained monomorphic VT, mean forearm blood flow was 2.2 ± 0.8 ml/min/100 ml ($p = 0.0002$ vs baseline) and mean forearm vascular resistance increased to 40 ± 14 units ($p = 0.01$ vs baseline). Forearm blood flow decreased to 2 ± 0.9 ml/min/100 ml during the first 30 seconds of sustained VT and to 2.6 ml/min/100 ml during the last 30 seconds of VT ($p = 0.02$, first 30 seconds vs last 30 seconds). Forearm vascular resistance increased to 41.3 ± 14 units during the first 30 seconds of VT and to 37 ± 13 units during the last 30 seconds of VT ($p = 0.15$, first 30 seconds vs last 30 seconds) (Figure 2). The individual values of each patient's forearm vascular resistance during the first and last 30 seconds of VT are shown in Figure 3.

Before intraarterial infusion of phentolamine, the mean arterial pressure, forearm blood flow and forearm vascular resistance returned to baseline. After infusion of phentolamine, forearm blood flow increased from 3.2 ± 1.1 to 8.7 ± 3.3 ml/min/100 ml ($p = 0.0004$ vs pre-drug baseline) and forearm vascular resistance decreased from 32 ± 14 units to 16 ± 6 units ($p = 0.02$ vs pre-drug baseline) (Figure 2). After reinduction of VT, there was a mean decrease in mean arterial pressure of 13 ± 5 mm Hg ($p = 0.03$ vs phentolamine baseline), and a decrease in systolic arterial pressure of 25 ± 9

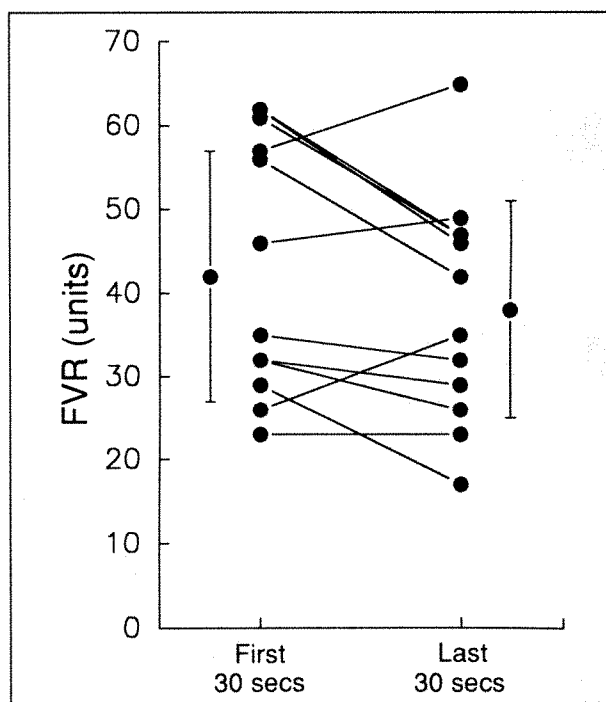


FIGURE 3. Individual values of forearm vascular resistance (FVR) for 11 patients measured during the first and last 30 seconds of sustained ventricular tachycardia. In 4 patients, there was an insufficient number of adequate forearm blood flow curves during the first or last 30 seconds to be included in this analysis.

mm Hg ($p = 0.03$ vs phentolamine baseline). The change in mean arterial pressure or systolic arterial pressure during the second induction of sustained VT was not different from the change in arterial pressure during the first episode of VT (predrug). A decrease in forearm blood flow of 1.4 ± 1 ml/min/100 ml ($p = 0.14$ vs predrug baseline) and increase in forearm vascular resistance of 2.8 ± 2 units ($p = 0.11$ vs predrug baseline) was observed during VT. The increase in forearm vascular resistance during VT with phentolamine was 66% less than was observed during the baseline ("unblocked") episode ($p = 0.01$).

DISCUSSION

Morady et al¹¹ have demonstrated previously that increases in plasma norepinephrine may occur during hemodynamically tolerated sustained VT. This study confirms these findings and extends these important observations to measurements of regional vascular tone and elucidation of the time course and mechanism for these responses. Our study demonstrates that vasoconstriction occurs rapidly, and is near maximal by the first 30 seconds of induced VT. Phentolamine, an α -adrenergic blocking drug, reduced vasoconstriction during VT by 60 to 70%. These observations show that VT induction is accompanied by abrupt and important changes of regional adrenergic sympathetic outflow.

A variable degree of hemodynamic impairment may occur during episodes of sustained VT. Elucidation of the autonomic changes that occur during VT has been limited by the inability to develop an animal model of sustained monomorphic VT that is reproducible. Instead, investigators have measured autonomic changes during ventricular pacing. These studies have suggested that arterial baroreflexes play a key role in the maintenance of regional and total systemic vasoconstriction during pacing-induced hypotension.^{12,13} These studies also have suggested a role for β -adrenergic augmentation of cardiac contraction and relaxation in maintenance of hemodynamic stability during ventricular pacing.¹⁴ There are few studies in man regarding measurement of changes in autonomic tone during ventricular arrhythmias. Geschwind et al¹⁵ showed that frequent premature ventricular complexes increase both the coronary sinus and antecubital vein plasma norepinephrine levels. Human sympathetic nerve responses to spontaneous and induced ventricular premature beats show bursts of muscle sympathetic nerve activity related to the degree of hypotension caused by the premature ventricular complexes.⁹

Relatively few studies have attempted to measure changes in sympathetic tone during sustained VT. Morady et al¹⁶ measured a 3-fold elevation in plasma norepinephrine and a 5-fold increase in plasma epinephrine 1 minute after direct current countershock of hypotensive ventricular tachycardia. However, direct current cardioversion may by itself cause norepinephrine release. In a second study, Morady et al¹¹ were able to demonstrate a 30 to 40% increase in plasma norepinephrine during clinically tolerated VT. It is interesting

to note that the magnitude of neurohumoral sympathetic excitation they measured is similar to the increase in forearm vasoconstriction we observed during VT. The time course of vascular changes after induction of VT is quite rapid, suggesting this response may be mediated by arterial baroreflexes.

Limitations: We studied sympathetic responses in only a single vascular bed. Sympathoexcitation may or may not occur in other regional vascular beds. We did not measure cardiac output, and therefore systemic vascular resistance could not be calculated. In addition, other factors—such as body position, medication or state of hydration—may alter the magnitude of regional vasoconstriction. Patients with more severe degrees of ventricular dysfunction may be less able to respond with sympathetic vasoconstriction during hypotension associated with VT.

Clinical implications: Our results suggest that most patients with inducible sustained VT will manifest sympathetic vasoconstriction. Why do patients exhibit variable degrees of hypotension during VT? It is possible that despite regional sympathetic activation, in many patients regional vasoconstriction in one or more beds is not adequate to return blood pressure to baseline. However, in this study, many patients were able to maintain adequate mean arterial pressure to prevent more severe symptoms during VT. We speculate that systemic α blockade or other treatments that inhibit vasoconstrictor mechanisms may have a deleterious effect in preventing some patients from maintaining vasoconstrictor responses to induced ventricular arrhythmias. Moreover, patients with heart failure have impaired baroreflexes, which may compromise their ability to induce baroreflex-induced sympathoexcitation. Finally, changes in blood pressure do not adequately characterize the autonomic response to sustained VT and other measures are needed to understand better the role of the autonomic nervous system in mediating the hemodynamic adaptations that occur during sustained VT.

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Usefulness of Disopyramide for Prevention of Upright Tilt-Induced Hypotension-Bradycardia

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Susceptibility to transient hypotension-bradycardia of neurally mediated origin has been attributed in part to accentuated afferent neural traffic arising from cardiopulmonary mechanoreceptors, and consequently, may be diminished by agents with anticholinergic and negative inotropic effects, such as disopyramide phosphate. This study assessed electrocardiographic and hemodynamic responses to upright tilt testing (alone or during isoproterenol infusion) before and after disopyramide therapy in 10 patients (age range 16 to 74 years) with recurrent syncopal episodes of neurally mediated origin. Untreated, syncope occurred at ≤ 7 minutes of tilt alone (6 patients) or tilt plus isoproterenol at ≤ 3 $\mu\text{g}/\text{min}$ (4 patients) and was associated with hypotension (mean arterial pressure, 40 ± 16 mm Hg vs baseline 76 ± 10 mm Hg, $p < 0.001$) and inappropriate heart rate slowing (mean heart rate, 59 ± 39 beats/min vs baseline 88 ± 18 beats/min, $p < 0.005$). After oral disopyramide 150 mg 3 times daily (mean plasma level, 3.0 ± 0.64 $\mu\text{g}/\text{ml}$), all patients tolerated 10 minutes of both tilt and tilt plus isoproterenol (maximum dose, 3 $\mu\text{g}/\text{min}$) without symptoms, hypotension (mean arterial pressure; tilt 1 min, 79 ± 7 mm Hg vs tilt 10 min, 77 ± 8 mm Hg, difference not significant) or bradycardia (mean heart rate; tilt 1 min, 81 ± 12 beats/min vs tilt 10 min, 83 ± 11 beats/min, difference not significant). Furthermore, during subsequent 20 ± 5 months of disopyramide therapy, all but 1 patient remain asymptomatic. Thus, oral disopyramide may be effective for preventing inducible and spontaneous neurally mediated syncope.

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Transient hypotension-bradycardia of neurally mediated origin is believed to be a common cause of syncope in man¹⁻³ and may be, in part, triggered by increased afferent neural traffic arising from accentuated ventricular and aortopulmonary mechanoreceptor activity.^{4,5} The latter may be the consequence of diminished ventricular volumes and/or enhanced ventricular contractile state, such as that which may occur during severe hemorrhage,⁶ after amyl nitrate⁷ or nitroglycerin administration⁸ or during catecholamine infusion.^{9,10} Alternatively, ventricular mechanoreceptor activity may be accentuated by increased left ventricular wall stress accompanying aortic stenosis or obstructive hypertrophic cardiomyopathy.¹¹ The outcome in each of these conditions is similar: hypotension occurs secondary to peripheral vascular dilatation and bradycardia occurs due to enhanced efferent parasympathetic tone. Symptomatic hypotension-bradycardia episodes may be either solitary or at most very infrequent, or they may be recurrent in some individuals; it has been postulated that even fatalities may occur.¹² Potentially, identification of effective prophylactic medications may be helpful in the most frequently affected individuals. Given the potential role of enhanced central mechanoreceptor activity and accentuated parasympathetic tone in hypotension-bradycardia syndrome, we postulated that the negative inotropic and anticholinergic effects of disopyramide phosphate (factors which often limit its usefulness as an antiarrhythmic agent) might diminish susceptibility to neurally mediated syncope. To this end, we examined the effect of orally administered disopyramide phosphate on inducibility of syncope in 10 patients known to exhibit hypotension-bradycardia syndrome in response to upright tilt provocation.

METHODS

Ten patients with recurrent unexplained syncope referred to the arrhythmia service of the University of Minnesota were evaluated with conventional medical and neurologic techniques. Syncope was defined as a clinical syndrome characterized by abrupt, transient loss of consciousness with inability to maintain postural tone. In 3 patients, there was documentation of concomitant prolonged asystole (16 to 21 seconds in duration) during loss of consciousness. All patients underwent a complete medical history, physical examination and routine laboratory testing. Postural vital signs were recorded in all patients and individual right and left carotid sinus massage was performed during continuous electrocardiographic monitoring. M-mode and 2-dimension-

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TABLE I Clinical Findings

Patient	Age (yrs)	Sex	Recurrent Syncope	Syncope During Exercise	Cardiac Arrest
1	26	M	0	+	+
2	17	M	0	+	0
3	27	M	+	0	0
4	28	F	+	0	0
5	16	F	0	+	+
6	36	M	+	0	0
7*	74	M	+	0	0
8	49	M	+	0	0
9	36	M	+	0	0
10	40	M	+	0	0

* Carcinoid syndrome.

al echocardiography was performed in all patients. Neurologic consultation was obtained in all patients.

Electrophysiology study: After obtaining informed consent, all patients underwent electrophysiology evaluation in the postabsorptive state after mild sedation with intravenous diazepam 5 mg. Antiarrhythmic drugs had been discontinued for at least 5 half-lives before electrophysiologic study. Using the percutaneous approach and modified Seldinger technique, three 6 Fr quadripolar electrode catheters were advanced via the right femoral vein and positioned at the high right atrium, right ventricular apex and across the tricuspid valve for His bundle recording. A cannula was placed percutaneously into the femoral artery to monitor arterial pressure. Surface electrocardiographic leads I, II, III, V₁, V₆, intracardiac recordings from the high right atrium, right ventricle and His bundle position, and arterial pressure were simultaneously displayed on an Electronics for Medicine VR16 recorder and recorded on FM tape (Ampex model PR 2230). For purposes of analysis, hard copy recordings were obtained at paper speeds of 50 or 100 mm/s.

Pacing was accomplished by means of a custom-designed programmable stimulator with optically isolated

outputs. The stimulus duration was 2 ms and the amplitude was set at twice diastolic threshold. Baseline atrioventricular nodal and infranodal conduction times were recorded. Sinus node function was assessed by determining sinus node recovery times at pacing cycle lengths ranging from 700 to 300 ms in 50-ms decrements. The subsequent 10 postpacing intervals were analyzed for the presence of secondary pauses. Atrioventricular nodal and infranodal conduction and refractoriness characteristics were determined both by right atrial pacing at progressively shorter cycle lengths and by extrastimulus testing using a drive train of 8 cycles at basic pacing cycle lengths 600 and 400 ms. Single atrial extrastimulus was introduced at 10 ms decrements until refractoriness was reached.

The protocol for ventricular stimulation included scanning of diastole with single, double and triple ventricular extrastimuli introduced after an 8-beat ventricular drive train at cycle lengths 600 and 400 ms. Ventricular extrastimulus testing was performed at both right ventricular apex and right ventricular outflow tract, with coupling intervals progressively shortened by 10 ms decrements until ventricular refractoriness was reached.

Patients in whom a cause of syncope was apparent from conventional electrophysiology testing were excluded from this study.

Upright tilt: Upright tilt testing was performed using an electronically controlled tilt table with a foot board for weight-bearing. After conventional electrophysiology testing was completed, baseline measurements of heart rate and blood pressure were recorded with the patient in the supine position. Each patient was then subjected to an 80° upright tilt for 10 minutes, with a positive response defined as development of syncope. If the patient did not have a positive response under baseline conditions, the patient was lowered to the supine position at the end of the 10-minute period. After a resting period of 5 minutes, upright tilt was repeated during

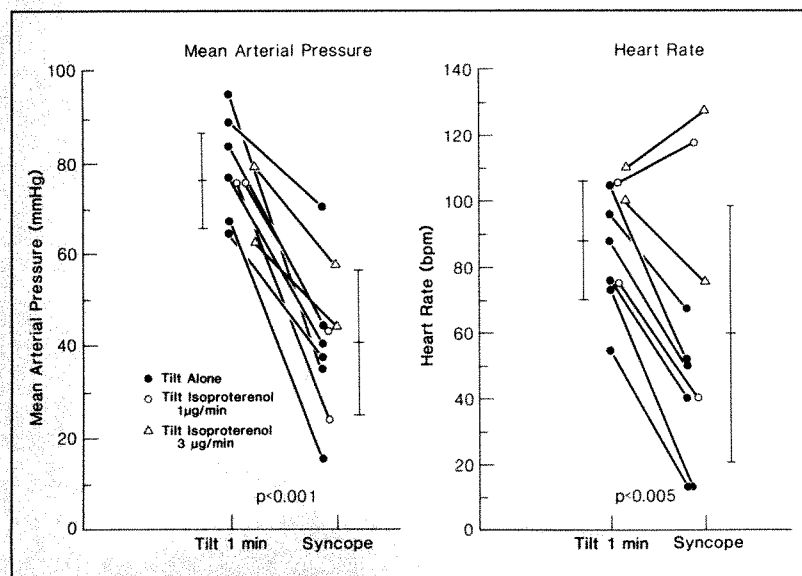


FIGURE 1. Mean arterial pressure (left) and heart rate (right) changes from 1 minute of upright tilt to time of development of syncope in each patient. All patients had dramatic decrease in mean arterial pressure; 8 of 10 had inadequate heart rate responses and 2 patients had increased heart rate during hypotension.

continuous intravenous isoproterenol infusion at successive incremental doses of 1 and, if necessary, 3 $\mu\text{g}/\text{min}$. During each step of the protocol, the patient was returned to the supine position either when a positive response was achieved or after 10 minutes of upright tilt.¹⁰ An equilibration period of 5 minutes during which heart rate and blood pressure were allowed to achieve a stable baseline value was introduced between each successive isoproterenol dose increase. Only patients exhibiting a positive response to upright tilt (with or without isoproterenol) were included in this study.

Disopyramide administration: In all patients, oral disopyramide phosphate therapy was initiated (150 mg 3 times daily). Forty-eight hours later, the response to upright tilt was reevaluated in the same electrophysiology laboratory at approximately the same time of day as the initial study and in a similar conventional pre-catheterization fasting state. A blood sample for disopyramide serum concentration was drawn.

Statistical analysis: Group data are reported as the mean $\pm$ standard deviation. Intraindividual comparisons were made using Student's *t* test for paired data. Statistical significance was assumed for a *p* value <0.05 .

RESULTS

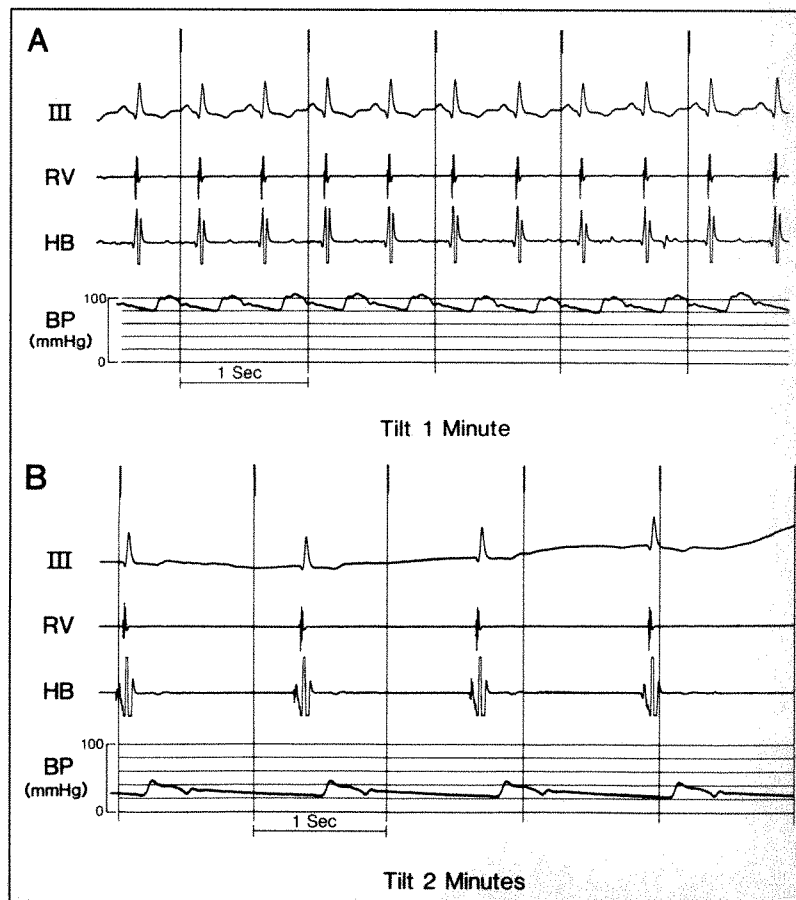
Clinical findings: Table I lists clinical findings in the patient population. No patient had evidence of underly-

ing structural heart disease or neurologic abnormalities. Patient number 7 had carcinoid syndrome and had reported several spells of facial "flushing" unassociated with syncope. In patients number 1, 5, 6 and 10, bradycardia or prolonged asystole had been implicated as the cause of syncope. Three patients (numbers 1, 2 and 5) had syncope during exercise.

Electrophysiologic findings: Eight patients had no electrophysiologic abnormalities. Patients number 2 and 9 exhibited findings suggestive of accentuated parasympathetic tone (sinus bradycardia and prolonged atrio-ventricular node effective refractory period that normalized after intravenous atropine administration). It should be noted that in the latter 2 patients, atropine was not administered until all baseline upright tilt studies were completed. None of the patients manifested inducible ventricular arrhythmias during programmed ventricular stimulation.

Response to upright tilt (before disopyramide): All patients included in the study developed syncope during upright tilt. In each case, compared to baseline arterial pressure measured 1 minute after assumption of upright posture, syncope was associated with a marked decrease in mean arterial pressure (baseline tilt 76 ± 10 mm Hg vs syncope 40 ± 16 mm Hg, *p* <0.001 , Figure 1). Further, the chronotropic response to this degree of hypotension was inappropriate; the mean heart rate for the group decreased from 88 ± 18 beats/min in the first

FIGURE 2. Electrocardiographic, intracardiac and arterial pressure recordings from patient number 5 showing heart rate and arterial pressure changes during upright tilt. From top to bottom in each panel are electrocardiographic lead III, right ventricular (RV) and His bundle (HB) electrograms and arterial pressure (BP). A, at 1 minute of upright tilt, mean arterial pressure was 90 mm Hg and heart rate 90 beats/min. B, at 2 minutes of upright tilt, the patient experienced syncope. Mean arterial pressure was 50 mm Hg and there was a junctional escape rhythm at a rate of 42 beats/min.



minute of tilt to 59 ± 39 beats/min during the syncope spell ($p < 0.005$, Figure 1). In only 2 of the 10 patients was there a modest positive chronotropic response, and in these individuals, hypotension was marked nonetheless.

Six patients (numbers 3, 4, 5, 8, 9 and 10) became syncopal during tilt alone; 5 within 5 minutes of assuming upright posture and 1 patient at 7 minutes of tilt. All patients had a dramatic decrease in blood pressure with inadequate heart rate response (Figures 1 and 2). Two patients (numbers 1 and 2) tolerated baseline tilt but became syncopal when tilt was undertaken during isoproterenol infusion at $1 \mu\text{g}/\text{min}$. These patients developed syncope within 3 minutes of assuming upright posture. In patient number 2, mean arterial pressure decreased from 75 to 42 mm Hg concomitantly with a decrease in heart rate from 75 to 42 beats/min. In patient number 1, a decrease in blood pressure from 100/50 to 35/15 mm Hg was associated with a modest but inadequate positive chronotropic response (105 beats/min at onset of upright tilt, 117 beats/min at time of syncope). Two patients (numbers 6 and 7) tolerated baseline upright tilt and tilt during isoproterenol infusion at one $\mu\text{g}/\text{min}$, but developed syncope during combined tilt and isoproterenol infusion at $3 \mu\text{g}/\text{min}$. Patient number 6 developed syncope at 2 minutes after assumption of upright posture with a decrease in mean arterial pressure from 78 to 57 mm Hg and a decrease in heart rate from 100 to 75 beats/min. Patient number 7 developed syncope at 6 minutes of tilt, with a decrease of mean arterial pressure from 62 to 43 mm Hg, despite a heart rate increase from 110 to 127 beats/min.

Response to tilt (after disopyramide): After 48 hours of oral disopyramide therapy (150 mg, 3 times daily), tilt studies were repeated under baseline conditions and, if necessary, during levels of isoproterenol infusion equivalent to those that had previously initiated syncope. Thus, isoproterenol was infused at $1 \mu\text{g}/\text{min}$ in patients number 1 and 2 and at $3 \mu\text{g}/\text{min}$ in patients number 6 and 7.

Figure 3 shows arterial pressure and heart rate changes during post-disopyramide upright tilt studies. Overall, there was no significant change in blood pressure or heart rate in response to tilt provocation and no patient developed syncopal symptoms. Mean disopyramide plasma levels, measured from blood samples obtained during tilt testing, were $3.0 \pm 0.64 \mu\text{g}/\text{ml}$.

Follow-up: Disopyramide therapy was continued after hospital discharge in all patients. During a follow-up period of 20 ± 5 months, all patients except patient number 4 remain asymptomatic. Patient number 4 continued having frequent recurrent presyncopal spells and frank syncope. Outpatient electrocardiographic recordings obtained during a syncopal episode (The Heart System, Survival Technology, Inc.) did not show heart rate abnormalities.

DISCUSSION

Neurally mediated hypotension and bradycardia is believed to be a frequent cause of symptoms in patients with syncope of unexplained origin.¹⁻³ The principal finding in this study was the demonstration that orally administered disopyramide phosphate diminished susceptibility to both induced and spontaneous development of symptomatic hypotension and bradycardia. This finding provides a potential therapeutic alternative for some patients with recurrent neurally mediated syncope.

The pathophysiologic basis of neurally mediated syncopal syndromes (e.g., vasovagal syncope, postmicturition syncope, cough syncope) is poorly understood. Studies in patients with inducible vasovagal reactions have shown heart rate increases before symptom onset, a finding suggestive of a transient premonitory increase in adrenergic tone.^{13,14} Indeed, although concomitant parasympathetic withdrawal has not been unequivocally excluded, elevation of circulating catecholamines has been noted before development of syncope in such patients.¹⁵ The occurrence of clinical symptoms during exercise or stressful situations in some of our patients is

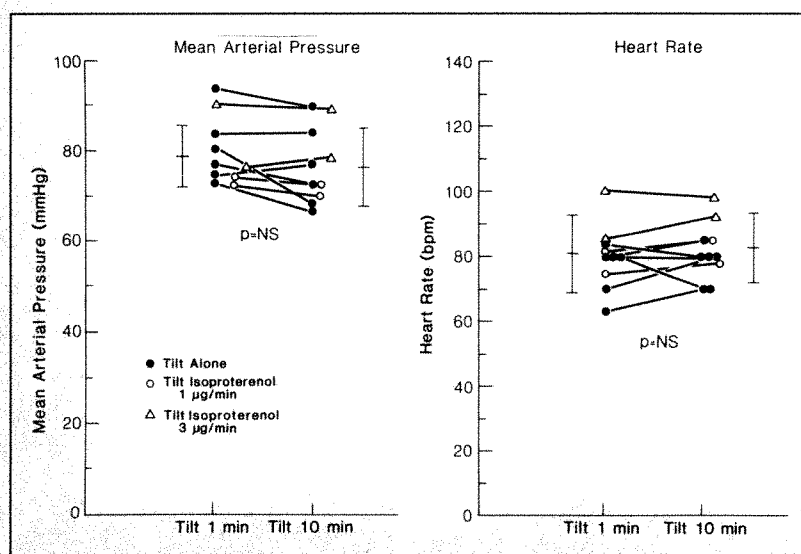


FIGURE 3. Mean arterial pressure (left) and heart rate (right) changes at 1 and 10 minutes of upright tilt after 48 hours of disopyramide therapy in each patient. Unlike before disopyramide treatment, there was no longer a statistically significant inducible arterial pressure or heart rate change with tilt provocation. NS = not significant.

supportive of the importance of a preceding increase in catecholamine levels, as is the observation that demonstration of susceptibility to hypotension-bradycardia may be facilitated by low-level catecholamine infusion.^{9,10} Catecholamine-induced peripheral β_2 -adrenergic agonist activity might explain both vasodilatation and hypotension.¹⁶ However, neither the magnitude of the hypotension nor the severity of bradycardia usually observed is readily explained on this basis.

It has been proposed that cardiopulmonary mechanoreceptors may play an important role in initiating the reflex responses associated with neurally mediated syncope.^{6,9,15,17} Normally, venous pooling associated with upright posture is compensated for by combined reflex tachycardia and venous and arteriolar constriction. Typically, in the setting of reduced venous return, cardiac mechanoreceptors exhibit diminished activity, thereby promoting reflex sympathetic stimulation. However, experimental evidence suggests that rapid loss of central volume (such as may occur with severe hemorrhage) can, especially in conjunction with the excitatory effects of increased circulating catecholamines, result in more vigorous contraction and increased neural traffic from left ventricular mechanoreceptors.⁶ This apparently "paradoxical" afferent neural traffic would promote reflex bradycardia and peripheral vascular dilatation.¹⁷ Alternatively, factors that diminish vigorous ventricular contraction would be expected to prevent both the resulting vasodepressor as well as the negative chronotropic response associated with this reflex.

Preliminary findings suggest that β_1 -adrenergic ("cardioselective") blocking drugs may be useful in preventing reflex hypotension-bradycardia, presumably based in part on their negative inotropic action.¹⁰ Potentially, agents that offer a vagolytic action may offer the advantage of diminishing efferent hypervagotonia associated with this reflex, and thereby blunt the severity of induced bradycardia, which may eventually lead to asystole.¹⁸ To this end, muscarinic blocking agents such as propanthine¹⁹ and belladonna alkaloids²⁰ have been shown to be helpful in some patients. Finally, drugs that increase peripheral vascular resistance have been shown to decrease the degree of vasodepressor hypotension induced in patients with carotid sinus hypersensitivity, a form of neurally mediated hypotension-bradycardia.²¹ Since disopyramide phosphate offers each of these pharmacologic actions to some degree, we postulated that it might be an effective oral agent for decreasing susceptibility to neurally mediated hypotension-bradycardia.

Disopyramide phosphate is a type IA antiarrhythmic agent with well-recognized potent anticholinergic effects and negative inotropic actions. Additionally, disopyramide may also tend to increase peripheral vascular resistance directly.²²⁻²⁷ Although the anticholinergic effect of disopyramide may be advantageous for preventing bradycardia associated with hypotension-bradycardia episodes, maintaining heart rate alone is often inadequate to prevent symptomatic hypotension.²¹ Indeed, the temporal sequence of events in our patients revealed

that hypotension preceded bradycardia in the majority of individuals.²⁸ Thus, hypotension alone, presumably due to peripheral vascular dilatation, might be sufficient to induce syncope in the absence of marked bradycardia in many patients. In fact, attempts to prevent bradycardia by atrial, ventricular or atrial ventricular sequential pacing in a few patients were ineffective. Nonetheless, vagolysis may play a role in decreasing severity of symptomatic hypotension in some individuals.

Identification of patients susceptible to neurally mediated hypotension-bradycardia by upright tilt testing has proved to be a useful diagnostic tool.^{9,10,18,20,28,29} Using this technique, findings in this study suggest that disopyramide phosphate may be a useful therapeutic modality in certain patients with recurrent neurally mediated syncope. The negative inotropic effects of disopyramide and an apparent tendency to increase peripheral vascular resistance have markedly limited the usefulness of this agent in many patients with cardiac arrhythmias and poor ventricular function. However, in the setting of this study, these aspects of disopyramide's pharmacology are fortuitous given the postulated basis of the hypotension-bradycardia syndrome.

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Increased Vagal Cardiac Nerve Traffic Prolongs Ventricular Refractoriness in Patients Undergoing Electrophysiology Testing

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Stimulation of the vagus nerve in animals causes prolongation of sinus cycle length, atrioventricular nodal conduction and ventricular refractoriness. Vagal stimulation appears to have a protective effect in animal models of sudden death. The electrophysiologic effects of enhanced vagal activity on right ventricular (RV) refractoriness in man have not been studied previously. The comparative effects of enhanced vagal tone (neck suction to -60 mm Hg) on sinus cycle length and RV refractoriness were assessed in 26 patients. The electrophysiologic effects of vagal activation by stimulation of carotid baroreceptors with neck suction were compared to the effect of carotid and aortic baroreceptor stimulation with phenylephrine infusion in 12 patients. During neck suction, mean sinus cycle length (819 ± 32 ms) was prolonged by 146 ± 20 ms ($p < 0.0001$). The mean RV effective refractory period (ERP) and functional refractory period (FRP) were prolonged by 4 ± 1 ms and 5 ± 1 ms ($p = 0.0001$ and 0.0002 , respectively). The mean change in RV ERP and FRP correlated with the peak change in sinus cycle length during neck suction ($r = 0.46$ and $r = 0.58$, respectively). During intravenous phenylephrine infusion, the mean change in RV ERP and FRP was 5 ± 2 ms ($p < 0.04$) and 10 ± 3 ms ($p < 0.01$), respectively.

These results show that reflex vagal stimulation with neck suction or phenylephrine infusion causes a small but significant prolongation in RV refractoriness. These findings imply that the potential benefits of enhanced vagal tone in preventing sudden death may be indirectly mediated by changes in ventricular refractoriness.

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The parasympathetic nervous system exerts important electrophysiologic effects on cardiac conduction and refractoriness.¹ Stimulation of the vagus nerve in animals and man shortens atrial refractoriness, and prolongs both atrioventricular (AV) node refractoriness and sinus cycle length.²⁻⁴ In addition to effects on AV conduction, the parasympathetic nervous system may also exert effects on the electrophysiologic properties of the ventricle.⁵

Vagal stimulation appears to enhance electrical stability of the ventricle since stimulation of the vagus nerve increases the ventricular fibrillation threshold.⁵⁻⁷ Conversely, infusion of isoproterenol facilitates induction of sustained ventricular arrhythmias in man and lowers the ventricular fibrillation threshold in animals.^{8,9} These effects may be related causally to changes in ventricular refractoriness. In dogs, vagal stimulation prolongs ventricular repolarization and refractoriness.¹⁰⁻¹² However, the electrophysiologic effects of enhanced vagal tone on right ventricular (RV) refractoriness have not been studied previously in man.

A functional role for parasympathetic influence on ventricular refractoriness has been suggested by previous studies using atropine.^{13,14} Assessment of parasympathetic influences by autonomic blockade with atropine is problematic, due to its multiple central and peripheral effects. We sought to assess directly the comparative effects of maximally tolerated enhanced vagal tone on sinus cycle length and RV refractoriness using maximally tolerated neck suction and phenylephrine infusion.

METHODS

We studied 21 patients referred for clinical electrophysiology study because of suspected or documented arrhythmias. An additional 5 patients were studied non-invasively with permanent pacemakers that were implanted at least 1 year before. One patient had an AFP 283 DDD pacemaker (Siemens-Pacesetter) and the other 4 had Spectrax 8420 or 5984 VVI pacemakers (Medtronic) and were studied using a Custom Censys (model 23475) pacemaker programmer (Medtronic), which was limited to decrementing coupling intervals by 8-ms steps. All patients were studied after giving verbal and written informed consent to a protocol approved by the Committees for the Conduct of Human Research at the Medical College of Virginia and the McGuire Veterans Administration Medical Center.

Electrophysiology study: Patients were studied in the fasting nonsedated state. All patients referred for

electrophysiology study had 2 or 3 quadripolar catheters (6 or 7Fr) introduced percutaneously through the femoral vein and positioned in the right atrial appendage, near the tricuspid valve to record a His bundle and in the RV apex under fluoroscopic guidance. Systemic arterial pressure was recorded from a 6 or 7Fr sheath in the femoral artery. Respiration was monitored by a bellows-type respirometer to indicate inspiratory and expiratory movements.

RV refractory periods were measured with a custom-designed, digital programmable stimulator (model DTU-201, Bloom Associates) and continuous recordings were made with a 16-channel physiologic recorder (VR-16, Electronics for Medicine) at a paper speed of 100 mm/s. Surface (I, II, III, V₁) and intracardiac electrograms (right atrial, His, RV) were displayed at standard filter settings. Pacing was performed at a pulse width of 2 ms with an amplitude of twice diastolic threshold throughout the study (<2 mA). All RV refractory periods were determined from the RV apex. In the pacemaker patients, RV refractory periods were determined using a programmable stimulator, or directly with a pacemaker programmer.

Study protocol: Before initiation of the study, the catheter in the RV apex was advanced as far distally as possible to ensure stable catheter position. Catheter position was checked often by fluoroscopy throughout the procedure.

Neck suction was performed with a custom-designed malleable padded collar and vacuum source capable of delivering negative atmospheric pressure of -60 mm Hg.¹⁵ The pressure gauge on the neck collar was calibrated with a mercury manometer before each study. Neck suction was manually activated and maintained for 5 seconds. We assumed that neck chamber pressures were transmitted faithfully to the carotid sinus. Peak RR interval responses to -60 mm Hg neck suction dur-

ing normal sinus rhythm were obtained first during held expiration (10 trials). Baseline neck suction responses of the sinus node could not be measured in 6 patients due to atrial fibrillation or frequent ventricular premature complexes. The 3 patients with heart block had permanent pacemakers and sinus cycle length could not be measured because their ventricular response was slower than the lowest programmable pacemaker setting. The RV refractory period was measured using a 8-beat drive train and an intertrain pause of at least 10 seconds. It was determined at baseline in triplicate, and then at a cycle length of 600 or 500 ms to minimize hemodynamic changes during ventricular pacing. If any determinations were more than 5 ms apart, the patient was excluded from further study (n = 4). All refractory period determinations were performed during held expiration to minimize the effects of catheter movement and variations in vagal activity related to respiration. Finally, all refractory period determinations were begun with a single extrastimulus (S₂) at least 20 ms longer than the previously determined refractory period. After the baseline determination of RV refractory period, the protocol was repeated in triplicate with and without maximal neck suction. We delivered -60 mm Hg neck suction triggered at the third to fourth paced QRS complex of each pacing drive train (Figure 1).

In 12 patients, RV refractory period was determined in duplicate during an infusion of phenylephrine that increased systolic arterial pressure by 20 to 30 mm Hg.

In an additional 6 patients, 0.2 mg/kg of intravenous propranolol was administered over 15 minutes. After a 5- to 10-minute rest period, the RV refractory period was determined in duplicate with and without neck suction.

Data analysis: We recorded on FM tape a surface electrocardiogram, bipolar atrial and ventricular electrograms, arterial pressure, neck chamber pressure and

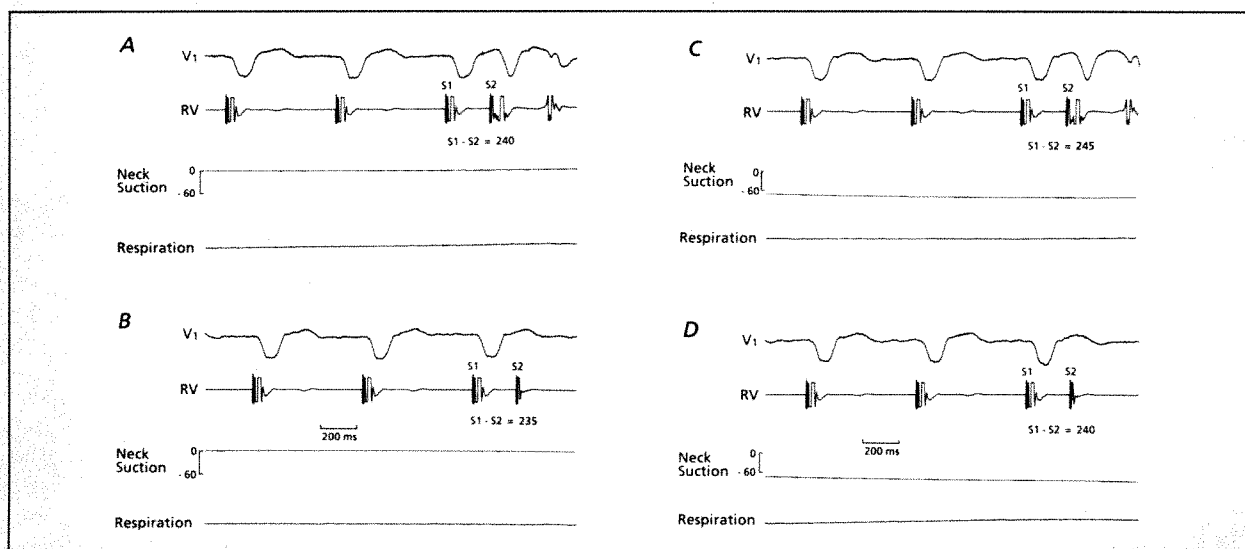


FIGURE 1. Standard electrocardiographic lead V₁, right ventricular (RV) endocardial electrogram, intracollar pressure and respiratory tracings are shown. Ventricular pacing at 600 ms was used to determine RV refractory period. In A and B, the RV effective refractory period without neck suction is 235 ms at baseline and the RV functional refractory period (not shown) is 255 ms. In C and D, the RV effective refractory period is measured and found to be 240 ms during neck suction at -60 mm Hg and the RV functional refractory period (not shown) is 260 ms.

respiration. Patients with frequent ventricular premature complexes, premature atrial contractions or other atrial arrhythmias were excluded from this analysis. We calculated sinus cycle length changes during the application of neck suction by determining the peak AA interval increase during the 5 seconds of neck suction. The results of 10 trials were averaged. AA intervals and RV refractory periods were calculated off line from the recorded surface or intracardiac electrograms with a digital computer (Hewlett Packard 1000). During each refractory period determination, the coupling interval of the extrastimulus (S_2) was decreased by 5 ms. The RV refractory periods were averaged independently with and without neck suction to provide mean values. The RV effective refractory period (ERP) was defined as the longest stimulus-to-stimulus interval that failed to evoke a ventricular response and the RV functional refractory period (FRP) was defined as the shortest ventricle-to-ventricle interval (measured from surface electrocardiogram or intracardiac RV electrogram) in response to any stimulus interval during RV pacing.¹⁶

Statistics: The changes in refractory period induced by neck suction or phenylephrine were analyzed by a paired *t* test. The relation of changes in refractory period during neck suction to peak pulse interval response to neck suction was assessed by linear regression. A *p* value of ≤ 0.05 was accepted as significant.

RESULTS

Patient population: We studied 26 male patients with a mean age of 56 ± 3.5 years. Fourteen patients had coronary artery disease and a previous myocardial infarction, 6 had dilated cardiomyopathy, 1 had valvular heart disease and 5 had no organic heart disease. Eighteen patients were not taking antiarrhythmic medications, while 6 were taking amiodarone, 1 procainamide and 1 quinidine. Fourteen patients were undergoing electrophysiologic testing for treatment of ventricular tachycardia, 3 for treatment of supraventricular tachycardia, 2 for nonsustained ventricular tachycardia, 2 for syncope and 5 for conduction system disease.

Response of sinus node to neck suction: The mean baseline sinus cycle length was 819 ± 32 ms ($n = 20$). This measure was not obtained in 6 patients; 3 had complete heart block, 1 had atrial fibrillation and 2 had frequent ventricular premature complexes or premature atrial contractions. The mean peak RR interval prolongation during neck suction was 146 ± 20 ms ($p < 0.001$).

Response of right ventricular refractory period to neck suction: The mean RV ERP at a cycle length of 600 ($n = 18$) or 500 ms ($n = 8$) was 272 ± 6.0 ms. During neck suction, the mean RV ERP was 276 ± 6 ms (Δ ERP 4 ± 0.6 ms, $p = 0.0001$). The mean FRP increased from 296 ± 6 to 301 ± 6 with neck suction (Δ FRP 5 ± 1 ms, $p < 0.0002$) (Figure 2). Eight patients had no change in RV ERP or FRP during any of the 3 trials of neck suction. The other 18 patients had maximal changes in RV refractory periods ranging from 5 to 25 ms in ≥ 1 trial of neck suction. For RV ERP, 11 patients had a maximal change of 5 ms during ≥ 1 neck

suction trial, 3 patients of 8 ms, 2 patients of 10 ms and 2 of 15 ms. For RV FRP, 13 patients had a maximal change of 5 ms during ≥ 1 neck suction trial, 3 patients of 10 ms, 2 patients of 15 ms, 1 patient of 20 ms and 1 patient of 25 ms.

In the 8 patients taking antiarrhythmic agents, the increase in RV ERP and FRP during neck suction was 4 ± 1 and 5 ± 1 ms, respectively (difference not significant compared to changes in RV ERP and FRP in patients not taking antiarrhythmic agents).

Figure 3 shows that the change in RV ERP and FRP during neck suction correlated with the peak change in sinus cycle length during neck suction ($r = 0.46$, $p = 0.05$ for ERP; $r = 0.58$, $p = 0.01$ for FRP). There was no correlation between the type of underlying heart disease or ejection fraction and the presence of a change in RV ERP or FRP with neck suction.

Phenylephrine response: Twelve consecutive patients received an intravenous infusion of phenylephrine (0.5 to 2.0 $\mu\text{g/kg/min}$), which resulted in an increase in systolic blood pressure of 24 ± 5 mm Hg and a prolongation in sinus cycle length of 95 ± 12 ms. The mean increase in RV ERP was 5 ± 2 ms ($p < 0.04$) and in RV FRP was 10 ± 3 ($p < 0.01$) during phenylephrine infusion. Nine of the 12 patients had a prolongation of RV ERP with phenylephrine; the maximal increase was 5 ms in 4 patients, 10 ms in 3 patients and 15 ms in 2 patients. Five of the 12 patients who received phenylephrine were also taking antiarrhythmic agents. The mean increase in RV ERP in these patients was 6 ± 3 ms and in RV FRP was 9 ± 3 ms (difference not significant compared to changes in RV ERP and FRP in patients not taking antiarrhythmic agents).

There was a greater prolongation of RV FRP with phenylephrine compared to neck suction ($p = 0.04$). The prolongation of RV ERP with phenylephrine was not different from that seen with neck suction alone ($p = 0.30$).

Propranolol response: In 5 patients after an intravenous infusion of propranolol, repeat baseline RV ERP and FRP were obtained before and after neck suction. In 3 of 5 patients, there was no change in RV refractory

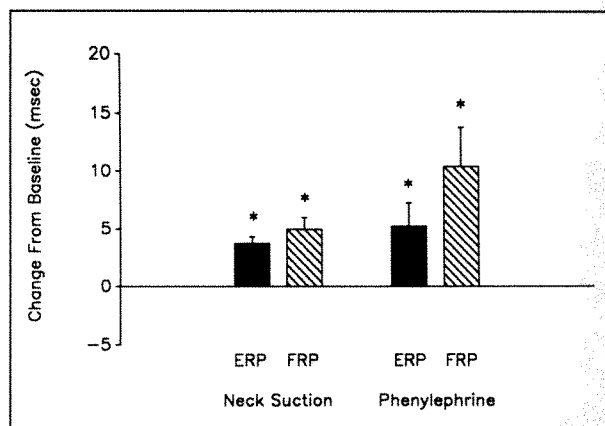


FIGURE 2. Bar graphs showing mean right ventricular effective refractory period (ERP) and functional refractory period (FRP) changes with neck suction and phenylephrine. * $p < 0.05$ vs zero.

periods with neck suction and in the other 2 patients there was a mean increase in RV ERP and FRP of 5 ms.

DISCUSSION

This study demonstrates directly that stimulation of carotid baroreceptors prolongs RV effective and functional refractory periods in humans by a small, but significant amount. Moreover, stimulation of carotid and aortic baroreceptors with acute elevations of arterial pressure also prolongs RV refractory periods. The degree of sinus cycle length prolongation with neck suction correlated with the average change in RV ERPs and FRPs measured during neck suction. These results provide inferential evidence that baroreceptor stimulation elicits parallel increases in vagal traffic in the sinus node and right ventricle.

Vagal effect on cardiac conduction: There is a large body of evidence demonstrating the anatomic presence and functional importance of cholinergic influences on sinus node automaticity and AV node conduction.¹⁻³ Cholinergic influences on the electrophysiology of the right ventricle have not been clearly defined. Anatomically, the sinus and AV node have a denser cholinergic

innervation than the ventricles.¹⁷ Although cholinergic innervation of the ventricular myocardium is relatively sparse, vagal innervation of the specialized His Purkinje conducting tissue in the right ventricle is somewhat denser.⁶

Prystowsky,¹³ Morady¹⁴ and their co-workers have shown that in patients pretreated with propranolol, RV refractory periods shortened after muscarinic cholinergic blocking doses of atropine. This was interpreted as an effect of the parasympathetic nervous system to prolong RV refractoriness. Both of these studies relied on cholinergic blockade to assess the functional importance of vagal activity on RV refractoriness. However, atropine exerts complex electrophysiologic effects, making it difficult to extrapolate direct information about vagal effects on the right ventricle.¹⁸⁻²⁴ Several investigations have shown that atropine stimulates vagal centers in the medulla,¹⁸ and nicotinic receptors in vagal ganglia.¹⁹ It also has direct effects on muscarinic receptors in pacemaker cells,²⁰ inhibits anticholinesterase²¹ and alters cardiostimulatory responses by presynaptic modulation of adrenergic transmission. Also, large doses of atropine cause sinus tachycardia, which is not explained simply on the basis of muscarinic blockade.²²

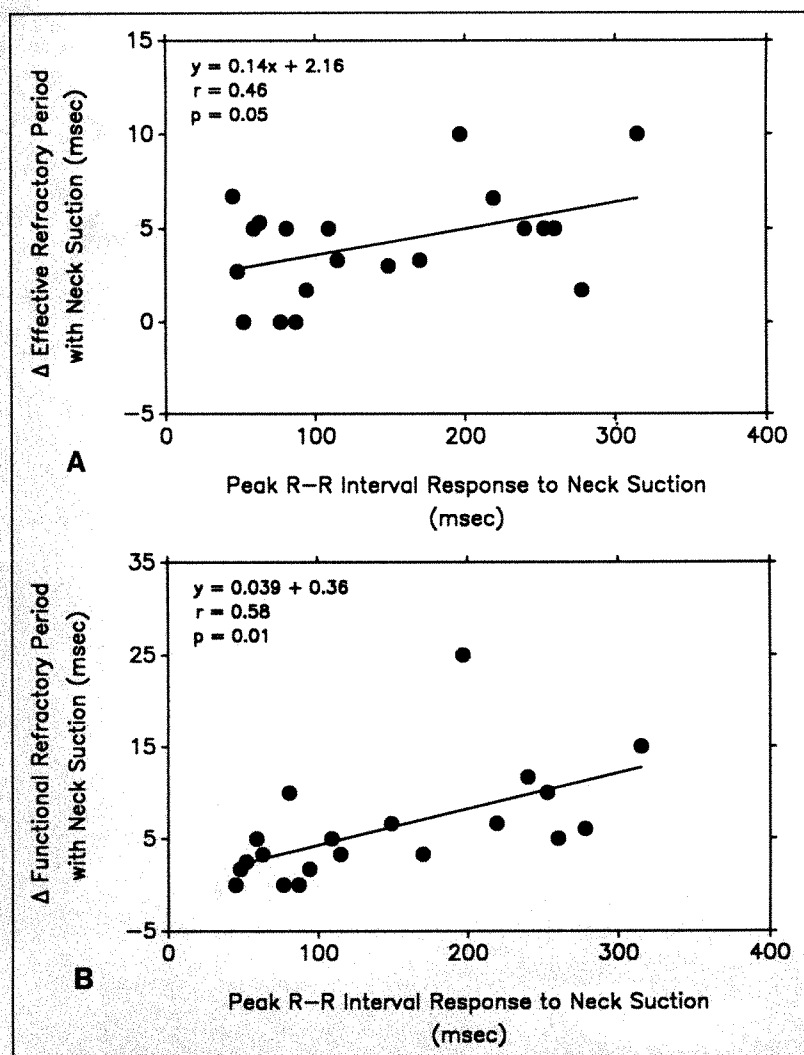


FIGURE 3. Linear regression demonstrating correlation between mean changes in right ventricular effective refractory period (A) and functional refractory period (B) with neck suction and peak change in sinus cycle length during neck suction.

Twelve patients received an infusion of phenylephrine to elevate arterial pressure, activating aortic, carotid and cardiopulmonary baroreflexes. Phenylephrine had a slightly greater effect on prolongation of RV refractory periods. A possible explanation for these findings might be that phenylephrine, through its activation of both aortic and carotid baroreflexes, causes a greater increase in vagal efferent activity and thus greater prolongation of RV refractory periods. Alternatively, these results may be explained by a direct α -adrenergic effect on the right ventricle.²³ In 1 study, phenylephrine prolonged isolated Purkinje fiber action potential duration,²³ although α -adrenergic stimulation with phenylephrine in anesthetized dogs did not affect RV refractoriness.²⁴ It is, therefore, possible that phenylephrine induced a prolongation of RV refractoriness resulting from both direct effects on the action potential and indirectly through activation of arterial baroreflexes.

Experimental protocol: Morady et al¹⁴ have noted a 5- to 10-ms variation between multiple determinations of ventricular ERP and FRP during electrophysiology study, but could not explain this finding. Several steps were taken to limit the variability of the estimation of RV refractory period. First, respiration was controlled (measurements made during held expiration) to minimize changes in vagal tone associated with respiration.²⁵ Second, each refractory period was begun with the S₂ at least 20 ms greater than the previous determined refractory period to minimize changes secondary to hysteresis.²⁶ Third, refractory periods were determined with and without neck suction in triplicate, with refractory periods directly juxtaposed to avoid time-dependent changes in ventricular refractoriness. In addition, only patients with RV refractory periods that demonstrated consistently less than 5 ms variability were included. We included 5 patients with permanent pacemakers in whom catheter movement would be an unlikely explanation for the small changes in refractory periods measured. Fourth, before pacing, catheter position was carefully checked to minimize small movements that might affect RV refractory period determinations.

Finally, we were surprised by the relatively small changes in refractory periods with neck suction compared to the magnitude of response noted by others after cholinergic blockade. The reason for this discrepancy is not clear, apart from the different methodologies used. We used -60 mm Hg neck suction, which is near maximal for carotid baroreflex activation in most patients (near saturation of the stimulus-response relation).²⁷ Furthermore, the mean changes in RV refractory period we measured were similar to those measured in dogs during carotid baroreceptor stimulation.¹⁰

Other investigators have noted a discrepancy between the electrophysiologic measurements made with cholinergic blockade and with enhanced vagal tone. For example, Dhingra et al²⁸ reported that atropine shortens atrial refractory periods after β blockade, implying that resting vagal tone prolongs atrial refractoriness. Prystowsky et al.⁴ however, showed that enhanced vagal tone delivered by a neck collar shortens atrial refractory periods.⁴ Therefore, electrophysiologic measurements

made after cholinergic blockade with atropine should not be considered equivalent to those made using neck suction to enhance vagal efferent traffic.

Clinical implications: Evidence from several groups of investigators indicate that cholinergic mechanisms may play an important role in ventricular dysrhythmias. The important studies of Schwartz,⁶ Kent²⁹ and their co-workers suggest that vagal stimulation may protect against ventricular fibrillation in a canine model. Waxman and Wald³⁰ described patients with ventricular tachycardia in whom vagal maneuvers consistently terminated ventricular tachycardia. In our study, direct vagal stimulation by neck suction or during phenylephrine infusion caused a highly significant prolongation of ventricular refractoriness. This electrophysiologic change may be one of the mechanisms by which vagal stimulation exerts a stabilizing effect on ventricular arrhythmias.

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Circadian Variation in Ventricular Electrical Instability Associated with Coronary Artery Disease

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Although sudden cardiac deaths and ischemic cardiac events clearly occur in a circadian pattern, such a pattern has not been shown for primary arrhythmic events. Because primary arrhythmic events are thought to play an important role in sudden cardiac death, a large series of ventricular stimulation studies was analyzed to determine whether circadian variation in ventricular electrical instability exists. If such a circadian variation could be shown, it could have implications for the conduct and interpretation of electrophysiologic testing and the etiology of circadian variation in sudden cardiac death. Results of 2 drug-free ventricular stimulation studies performed 4 to 28 hours apart in each of 162 patients with coronary artery disease were analyzed. Rate and duration of induced arrhythmia, number of extrastimuli required to induce arrhythmia and changes in these factors between the 2 tests in each patient were analyzed. Comparisons were made by half-day, by hour and in a temporally continuous manner to eliminate errors associated with any single method. No significant circadian variation was found in any electrophysiologic measure of ventricular electrical instability despite adequate statistical power.

These findings show that the time of day during which ventricular stimulation tests are performed does not affect test results, and therefore does not need to be controlled during electrophysiologic studies. If these findings are parallel to those in ambulatory patients with coronary artery disease, then circadian changes in ventricular electrical instability may not play as important a role in the circadian pattern of sudden cardiac death as had been previously thought.

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The majority of arrhythmic sudden cardiac deaths are thought to begin as primary arrhythmic events or as events secondary to ischemia. While sudden death^{1,2} and primary ischemic events³ have been shown to occur in a circadian pattern, no such pattern has been shown for primary arrhythmic events. Because primary arrhythmic events account for an important portion of all sudden cardiac deaths,⁴ but have not yet been shown to occur in a circadian pattern, we investigated whether temporal variation in ventricular electrical instability exists that could serve as the basis for a circadian pattern of arrhythmic sudden death. If such a variation exists, it could be responsible for part of the circadian variation in sudden cardiac death. If such a variation is absent, then other factors would be required to explain circadian variation in sudden cardiac death. In addition, circadian variation in the results of ventricular stimulation studies could have implications for the conduct and interpretation of these tests.

Investigation of circadian variation in ventricular electrical instability has previously used review of death certificates or continuous ambulatory electrocardiographic recording. Each of these methods has limitations. We used another method by investigating ventricular electrical instability through analysis of a large series of ventricular stimulation studies. These studies are uniquely suited to this analysis, as changes in the stability of the electrophysiologic substrate alone are evaluated while variations in the frequency of initiators of arrhythmic events, such as ischemia and ventricular ectopy, are controlled. In addition, temporal inaccuracies and reporting biases, problems that may hamper analysis of circadian patterns under less well-controlled circumstances, are eliminated.

METHODS

Patients: Between 1985 and 1988, 222 patients with coronary artery disease underwent electrophysiologic evaluation of serious ventricular arrhythmia at Oregon Health Sciences University; these electrophysiologic tests were analyzed retrospectively in this study. Patients were excluded from analysis if the times of their tests were not clearly recorded ($n = 31$) or if they required ongoing antiarrhythmic therapy or a β -blocking medication ($n = 29$). Patients requiring β blockers were excluded because these agents are thought to reduce circadian variation in cardiac events.^{1,5} The remaining 162 patients each underwent 2 drug-free ventricular stimulation studies 4 to 28 hours apart. Table I lists the clinical

TABLE I Patient Characteristics

	Group 1	Group 2	Group 3	Total	p Value
No. of patients	55	47	60	162	
Age (yrs)	56 ± 14	60 ± 13	57 ± 14	58 ± 12	NS
Sex (M/F)	48/7	36/11	52/8	136/26	NS
Presenting arrhythmia					
Nonsustained ventricular tachycardia	3	4	2	9	
Ventricular tachycardia	21	21	26	68	
Ventricular fibrillation	31	22	32	85	0.7

Group 1 = test 1 before noon and test 2 after noon; Group 2 = test 1 after noon and test 2 before noon; Group 3 = both tests before noon or both tests after noon.
NS = not significant.

TABLE II Categorization of Rate and Duration of Arrhythmia

Arrhythmia	Category
None	1
1 to 3 repetitive ventricular responses	2
4 to 6 beats of nonsustained ventricular tachycardia	3
>6 beats of nonsustained ventricular tachycardia	4
Sustained ventricular tachycardia, rate 100 to 160 beats/min	5
Sustained ventricular tachycardia, rate 161 to 200 beats/min	6
Sustained ventricular tachycardia, rate 201 to 300 beats/min	7
Sustained ventricular tachycardia, rate >300 beats/min or ventricular fibrillation	8

cal characteristics of these patients, grouped by time of day at which their studies were performed. Informed consent was obtained from each subject.

Definitions: Three patient groups were defined to facilitate pairwise analysis of morning and afternoon tests. Group 1 is made up of patients who underwent test 1 (the first test) in the morning and test 2 (the second test) in the afternoon. Group 2 is made up of patients who underwent test 1 in the afternoon and test 2 the following morning. Group 3 is made up of the remaining patients in whom both studies were performed in the morning or both in the afternoon.

Repetitive ventricular response was defined as an induced ventricular depolarization after the last captured ventricular pacing stimulus; nonsustained ventricular tachycardia as >4 repetitive ventricular responses and <30 seconds of self-terminating ventricular tachycardia; sustained ventricular tachycardia as ventricular tachycardia persisting for >30 seconds or requiring intervention due to hemodynamic instability; and ventricular fibrillation as completely disorganized ventricular electrical activity associated with hemodynamic instability.

Ventricular stimulation protocol: Our ventricular stimulation protocol has been previously described in detail.⁶ Two drug-free studies are performed in each patient; the first (test 1) uses 2 right ventricular pacing sites and 2 paced cycle lengths, with up to 4 programmed extrastimuli. Pacing proceeds from the right ventricular apex using 1, 2 and 3 extrastimuli before pacing using another catheter at the right ventricular outflow tract. Lidocaine (1/2%) is used for local anesthesia during the first study. A second study (test 2) is performed 4 to 28 hours later in the cardiac care unit using a right subclavian pacing catheter that is retained from the first study. Patients are fully ambulatory between the studies. Aside from pacing at only the apical site and the lack of local anesthesia, the second study follows a pacing protocol identical to that of the first.

The time at which each study is performed is based solely on scheduling concerns and bears no relation to patient characteristics.

Data collection: The hour and minute at which pacing began was recorded during each ventricular stimulation study. An electrocardiogram is recorded continuously during each study and induced arrhythmia is recorded on a standardized form. Each arrhythmic response is assigned an arrhythmia category based on the number of repetitive ventricular responses and the rate of tachycardia (if sustained) using a previously reported categorization system⁶ (Table II). The highest category attained during single extrastimulus technique with either cycle length is entered into a computerized database as the induced arrhythmia. The same is done for double, triple and quadruple extrastimuli technique. A complete ventricular stimulation study therefore results in assigning an arrhythmia category for the results of pacing with each of 1, 2, 3 and 4 extrastimuli. The highest of these categories is taken as the arrhythmia category for the entire test. This system allows analysis of traditional clinical endpoints, such as nonsustained or sustained ventricular tachycardia, as well as rates of sustained tachycardia and duration of nonsustained tachycardia. It also allows for pairwise analysis of arrhythmia induction and electrophysiologic studies can be compared as though <4 extrastimuli were used by limiting the analysis to the results obtained during single, double or triple extrastimulus technique.

Data analysis: Temporally continuous data were analyzed using harmonic regression analysis and the F test, nominal data were analyzed using chi-square analysis and ordered categorical data were analyzed using ridit analysis and the Mann-Whitney-Wilcoxon or Kruskal-Wallis test. Pairwise analyses were used whenever appropriate. No adjustments were made for multiple comparisons; all p values therefore represent "per comparison" values. Statistical values and equations

were derived using a commercial software package and a microcomputer. A p value of ≤ 0.05 was considered statistically significant.

Because patterns of circadian variation may be subtle, we analyzed the magnitude and direction of trends in the data, even when not statistically significant. We felt that these trends could be of importance if, for example, most or all trends were in the same direction. This could indicate that a relation is present, but a larger sample size is required to attain statistical significance. Conversely, if trends were small and without consistent direction, a larger sample would be unlikely to show an important relation. Much of the data is of the ordered categorical type; riddit analysis has been proposed as the method of choice for analyzing trends in this type of data.^{7,8} Mathematically closely related to the Mann-Whitney-Wilcoxon and Kruskal-Wallis tests, riddit analysis yields p values and other statistics identical to these tests.⁹ In addition, it extracts information concerning the direction and magnitude of differences in distribution among categories and may thereby be helpful in identifying subtle patterns and trends. A group's mean riddit is an estimate of the likelihood that a patient selected at random from that group will belong to a category that is of equal or higher rank than that of a patient drawn at random from a comparison group. For example, if a group's mean riddit is 0.75, there is a 75% likelihood that a patient selected at random from that group will belong to a category of equal or higher rank than a patient selected from the comparison group.

RESULTS

Equivalence of arrhythmia induction during tests 1 and 2: Unequal temporal distribution of tests 1 and 2 could confound the analysis if the tests differ in their capacity to induce arrhythmia. For example, if the first test always occurred in the morning and the second test always occurred in the afternoon, differences in arrhythmia induction between the 2 tests could be erroneously interpreted as differences in arrhythmia induction between the 2 time periods. The timing of tests is not uniformly distributed throughout the day; test 1 is most often performed between 10 A.M. and 3 P.M. while test 2 has a bimodal distribution with peak frequencies at 9

TABLE III Comparison of Tests 1 and 2

Duration of induced arrhythmia				
	Test 1	Test 2	Total	p Value
0 RVRs	2	4	6	
1 to 3 RVRs	37	44	81	
4 to 6 RVRs	14	13	27	
NSVT	20	18	38	
Sustained VT or VF	89	83	172	
Total	162	162	324	
Mean riddit:	0.51	0.49		>0.3*
Rate of sustained VT (beats/min)				
100 to 160	5	3	8	
161 to 200	23	19	42	
201 to 300	40	41	81	
>300 or VF	21	20	41	
Total	89	83	172	
Mean riddit	0.49	0.51		>0.5*
No. extrastimuli required to induce sustained VT				
1	12	7	19	
2	37	37	74	
3	24	22	46	
4	16	17	33	
Total	89	83	172	
Mean riddit	0.49	0.51		>0.5*

* Mann-Whitney-Wilcoxon test.
NSVT = nonsustained ventricular tachycardia; RVR = repetitive ventricular response; VF = ventricular fibrillation; VT = ventricular tachycardia.

A.M. and 6 P.M. Because the unpaired analyses depend on tests 1 and 2 being substantially equal in capacity to induce arrhythmia, results from these tests were compared to determine if they differ in this regard. There are no significant differences between tests 1 and 2 in duration or rate of induced arrhythmia or number of extrastimuli required for induction of sustained ventricular tachycardia (Table III).

Temporal variation in induction of arrhythmia: To avoid errors associated with any single method, temporal variation in arrhythmia induction was analyzed in the following 3 ways: continuously, by hour and by half-day.

TEMPORALLY CONTINUOUS ANALYSIS OF INDUCTION OF SUSTAINED VENTRICULAR TACHYCARDIA: Harmonic regression analysis was used to derive an equation relating the probability of induction of sustained ventricular tachycardia to the time at which the test was performed. The time of day (to the nearest minute) was

FIGURE 1. Induction of sustained ventricular tachycardia is shown for each hour in which tests were performed. Width of each bar is proportional to number of tests performed during the hour. Height of each bar represents percentage of tests in which sustained ventricular tachycardia is induced. Because few patients were tested between 8 P.M. and midnight, they are grouped together in the last bar.

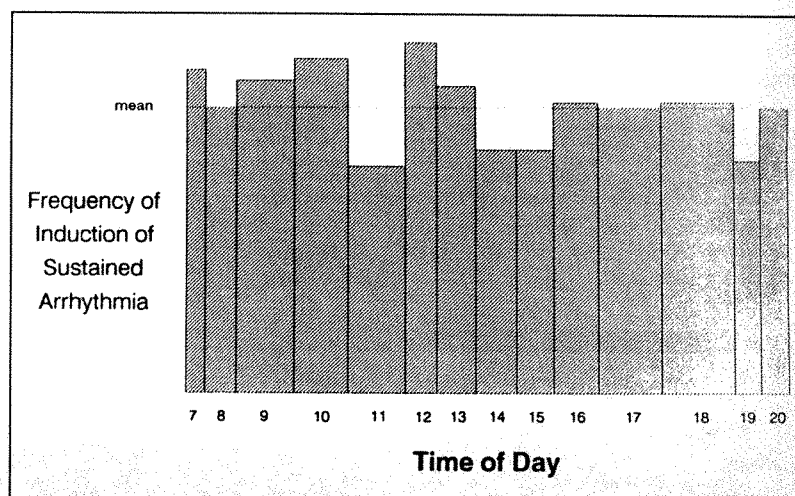


TABLE IV Comparison of Inducibility Before and After Noon

	Before Noon	After Noon	Total	p Value
Frequency of induction of sustained ventricular tachycardia				
Not induced	54	98	152	0.8
Induced	64	108	172	
Duration of induced arrhythmia				
0 RVRs	1	5	6	>0.7*
1 to 3 RVRs	32	49	81	
4 to 6 RVRs	5	22	27	
NSVT	16	22	38	
Sustained VT or VF	64	108	172	
Mean riddit	0.51	0.50		
Rate of sustained VT (beats/min)				
100 to 160	2	6	8	>0.4*
161 to 200	17	25	42	
201 to 300	26	55	81	
>300 or VF	19	22	41	
Mean riddit	0.52	0.49		
No. extrastimuli required for induction of sustained VT				
1	3	16	19	0.06*
2	25	49	74	
3	24	22	46	
4	12	21	33	
Mean riddit	0.55	0.47		

* Mann-Whitney-Wilcoxon test.
Abbreviations as in Table III.

used as the independent variable and induction of sustained ventricular tachycardia was used as the dependent variable in the following equation: $P[I] = 0.53 + (0.001)\cos(\pi t/12) + (0.001)\sin(\pi t/12)$. $P[I]$ represents the probability of induction of sustained ventricular tachycardia and t represents the time of the test in hours. The coefficients of the sine and cosine terms are not statistically different from zero (F test); that is, there is no time of day when the induction of ventricular tachycardia occurs significantly more frequently than the mean rate of induction.

HOURLY VARIATION IN INDUCTION OF SUSTAINED VENTRICULAR TACHYCARDIA: The percentage of tests in which ventricular tachycardia was induced during each hour of testing is shown in Figure 1. No hourly induction rate is significantly different from the mean daily frequency of induction. The smallest p value for this difference is noted for the hour between 11 A.M. and noon (chi-square = 1.0, $p = 0.32$), when the incidence of induction was reduced to 42%; all other p values exceeded 0.46.

INDUCTION OF ARRHYTHMIA BEFORE NOON VERSUS AFTER NOON: When tests performed in the morning are compared to tests performed in the afternoon, there is no significant difference between frequency of induction of sustained ventricular tachycardia, duration-related arrhythmia categories, rate of induced tachycardia or number of extrastimuli required for the induction of sustained ventricular tachycardia (Table IV). Riddit analysis shows statistically insignificant trends toward longer induced arrhythmias, faster rates and greater number of extrastimuli required for arrhythmia induction in the morning compared to the afternoon.

PAIRWISE COMPARISON OF DIFFERENCES IN INDUCTION BETWEEN TESTS 1 AND 2: If it were true that electrical in-

stability is greater in the morning than the afternoon, then one would expect arrhythmia categories to reflect a decrease in the severity of arrhythmia between tests 1 and 2 in group 1 patients (who were first studied in the morning) and an increase between the 2 tests in group 2 patients (who were first studied in the afternoon). The rates of induced arrhythmia and numbers of extrastimuli required for arrhythmia induction would be expected to reflect this difference in electrical instability in a similar fashion. This pairwise analysis is listed in Table V; changes in induced arrhythmia were calculated by subtracting the arrhythmia category (listed in Table II) attained during test 2 from the arrhythmia category attained during test 1 in the same patient. There is no statistically significant difference between any of the 3 groups with respect to changes in any of these parameters. In addition, the mean riddit values do not reflect any consistent trend.

DISCUSSION

In these 162 patients with coronary artery disease presenting for evaluation of serious ventricular arrhythmia, there is no detectable circadian variation in ventricular electrical instability between the hours of 7 A.M. and 11 P.M. as assessed by ventricular stimulation studies. No significant variations are present in the duration of induced arrhythmia, frequency of induction of sustained ventricular tachycardia, rate of induced tachycardia, "ease of induction" as measured by number of extrastimuli required for induction or changes in these parameters between consecutive ventricular stimulation tests in the same patient. Trends in one direction or the other are small. No circadian variations are found when patients are grouped by presenting arrhythmia or gender. Although not presented here, analysis after exclu-

TABLE V Pairwise Analysis of Differences in Induction of Arrhythmia Between Tests 1 and 2

	Category Change	Group 1	Group 2	Group 3	p Value
Change in duration of induced arrhythmia	-3	0	3	1	
	-2	0	0	1	
	-1	7	5	5	
	0	34	28	43	
	+1	9	7	6	
	+2	4	1	0	
	+3	1	3	4	
Mean ridit		0.52	0.49	0.47	>0.9*
Change in rate of induced tachycardia	-1	4	4	5	
	0	17	14	18	
	+1	3	0	4	
		0.52	0.44	0.52	
Mean ridit					>0.5*
Change in no. of extrastimuli required to induce VT	-2	1	3	1	
	-1	7	2	9	
	0	11	10	13	
	+1	4	2	3	
	+2	1	1	1	
		0.52	0.50	0.48	
Mean ridit					>0.9*

* Kruskal-Wallis test.

sion of test results obtained using 4 extrastimuli also failed to detect a circadian variation in ventricular electrical instability.

These findings are of interest for several reasons. First, they suggest that the time of the study does not need to be controlled during ventricular stimulation tests. Second, ventricular electrical instability, as assessed by the technique that we use clinically for this purpose, has no discernible circadian variation. This is true even though factors other than the pacing protocol itself were left uncontrolled during this study. This finding is concordant with investigations of ventricular electrical instability using the other primary means for assessing ventricular electrical instability—continuous ambulatory electrocardiographic monitoring (see discussion). Most interestingly, if these data apply to non-hospitalized persons with coronary artery disease, they suggest that changes in ventricular electrical instability may not play an important role in the known circadian variation in the onset of sudden death.

Analytic methods for the detection of circadian variation in ventricular electrical instability: Previous investigations of circadian variation in arrhythmic events have used review of death certificates or continuous ambulatory electrocardiographic recording. The earliest reports using electrocardiographic monitoring compared sleeping and waking hours and showed increased ectopy during certain phases of sleep.¹⁰⁻¹² Subsequent studies of sleep cycles have shown no difference in the frequency of arrhythmia between sleeping and waking hours¹³ or a marked decrease during sleep.^{14,15} Studies of 24-hour cycles of ventricular ectopic activity showed that peaks were either nonexistent,¹⁶ absent for simple ventricular ectopy but present for nonsustained ventricular tachycardia,¹⁷ unimodal at 7 A.M.,¹⁸ unimodal with a peak between 8 P.M. and midnight⁵ or bimodal with peaks at 8 A.M. and 4 P.M.¹⁹ or 11 A.M. and 9

P.M.²⁰ Others have shown that the incidence of symptomatic ventricular arrhythmias peaks near 11 A.M.²¹ The factors underlying these inconsistent findings are not entirely clear, although the well-described spontaneous variability of ventricular ectopic activity is likely to be a factor.^{22,23}

Reviews of death certificates have clearly shown circadian variation in the incidence of all forms of sudden death taken together.^{1,2} Hinkle and Thaler have shown that death certificates discriminate poorly between primary arrhythmic deaths and arrhythmic deaths secondary to myocardial ischemia. In their review of 142 sudden deaths, 41% of those deaths classified as arrhythmic in whom an autopsy was performed had evidence of acute occlusion of a major coronary artery.⁴ More than 75% of these were clinically "silent," indicating that clinical findings available to those completing death certificates may not be helpful in distinguishing between primary ischemic and primary arrhythmic events.

A major difference between our study and others is the use of a third method, ventricular stimulation studies, for the evaluation of circadian changes in ventricular electrical instability. Errors associated with accurate categorization and timing of the events are avoided using this method. These errors may introduce a systematic bias that results in showing circadian variations that do not truly exist or in the obscuring of true circadian relation. In particular, there has been concern that the well-documented morning increase in the frequency of cardiac events may be a manifestation of delayed discovery and reporting of events that occur between midnight and 6 A.M., when patients and observers are likely to be asleep. This delay would falsely decrease the apparent frequency of very early morning events and falsely increase the apparent frequency of events after 6 A.M. These potentially serious limitations to circadian analysis have been discussed in full by others.²⁴ By us-

ing electrophysiologic tests, we have been able to investigate changes in ventricular electrical instability in isolation from changes in the frequency of triggers of arrhythmia and acute ischemic events.

IMPLICATIONS FOR THE DETERMINANTS OF CIRCADIAN VARIATION IN THE ONSET OF SUDDEN CARDIAC DEATH: Studies based on continuous ambulatory electrocardiographic monitoring have shown that ectopic activity does not follow a consistent circadian pattern, and does not parallel the pattern of sudden death as determined by Muller and Willich and their co-workers.^{1,2} Our study also supports this lack of circadian variation in ventricular electrical instability. Sudden death does appear to follow a circadian pattern similar to that of acute myocardial infarction; if electrical instability of these patients parallels that of ambulatory patients, our study supports the concept that circadian variation in the incidence of sudden cardiac death may be primarily a manifestation of the well-documented circadian variation in primary ischemic events alone.

Limitations: The lack of circadian variation in induction of arrhythmia during ventricular stimulation studies does not preclude all circadian variation in ventricular electrical instability in these or other patients for the 4 reasons that follow.

METHODOLOGIC DIFFERENCES EXIST BETWEEN THE FIRST AND SECOND TESTS: Ideally, for statistical purposes, the conduct of the first and second tests should be identical. In our study, the first test occurred in the catheterization laboratory, shortly after the insertion of electrode catheters, whereas the second test occurred at the bedside using an indwelling catheter and the stimulation protocols were identical only through 3 extrastimuli. Lidocaine (½%) was used during the first test, but not the second. Reanalysis of the data using only results from the first 3 extrastimuli, which eliminates differences in stimulation techniques between the tests, did not substantially change the findings. The effects of methodologic differences on test results are listed in Table III; they are not statistically significant. That pacing from a second site should play a minor role in arrhythmia induction is supported by the findings of Kudenchuk et al who showed that stimulation from multiple right ventricular sites results in only a small increment in arrhythmia induction.²⁵

CIRCADIAN VARIATION IN ELECTRICAL INSTABILITY MAY BE ABOLISHED IN HOSPITALIZED PATIENTS: A number of studies support the concept that hospitalization alone does not abolish the circadian variation of human physiologic parameters.²⁶ It has been shown that circadian variation in some physiologic variables, such as renal excretion of water and electrolytes, may be lowered in amplitude by severe restriction of activity, but the circadian pattern persists.²⁷ Patients in this study were hospitalized but they were not acutely ill; for that reason we suspect that their circadian rhythms remained largely intact. If circadian rhythms had been disturbed by the electrophysiologic testing itself, however, their detection would be difficult or impossible using this method.

CIRCADIAN VARIATION MAY BE PRESENT, BUT TOO SUBTLE TO DETECT: In the largest study of sudden death, a

33.8% increase in incidence was reported during the 6 hours before noon as compared to the 6 hours after noon.¹ Based on our mean induction rate of 53%, induction would have to decrease from 63% in the morning to 42% in the afternoon to attain a change of that magnitude. To attain an 80% probability of detecting such a change with a 1-tailed test and a p value of 0.05, 220 observations are required²⁸; 324 observations are available in our study.

THE HOURS BETWEEN MIDNIGHT AND 7 A.M. WERE NOT OBSERVED: Because no tests were performed between midnight and 7 A.M., cyclic variation in ventricular electrical instability during those hours would not be detected by our study. Investigators of sudden cardiac death have found peak frequencies to occur during the late morning, however, when many of our tests were performed.

Conclusions: Our study shows that the time of day at which ventricular stimulation studies are performed does not affect induction of ventricular arrhythmia. Therefore, from a practical standpoint, it is not a variable that needs to be controlled during serial drug testing. In addition, if these results reflect the state of ventricular electrical instability in nonhospitalized patients with coronary artery disease, then primary arrhythmic events may be a less important component of the circadian variation in sudden death than previously thought.

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Validity of Arm Ergometer Blood Pressures Immediately After Exercise

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It is not possible to assess blood pressure (BP) by the standard cuff method during exercise primarily involving the arms. Consequently, such measurements are often taken immediately after (within 15 seconds) exercise. To assess the validity of this practice, 18 healthy men (mean age 32 years) who completed 3 progressive 3-minute workloads were studied during arm-crank ergometry. Ankle systolic BP was measured at the dorsalis pedis artery at seated rest, 15 seconds before completion of each exercise stage and immediately after each workload, using a Doppler stethoscope; simultaneous postexercise brachial systolic BPs were determined by auscultation. Brachial systolic BP during arm-crank ergometry was estimated by the formula: (resting brachial systolic BP) + (exercise ankle systolic BP - resting ankle systolic BP). Brachial systolic BPs, obtained immediately after arm-crank ergometry, were significantly lower than those estimated during exercise ($p < 0.001$), with corresponding mean values of 141 versus 153, 144 versus 173 and 151 versus 182 mm Hg at 150, 300, and 450 $\text{kg} \cdot \text{m} \cdot \text{min}^{-1}$, respectively. The difference between measured (postexercise) and estimated pressures increased with progressive workloads. These findings indicate that systolic BPs taken by the standard cuff method immediately after arm-crank ergometry are likely to underestimate "true" physiologic responses.

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Although the methodology of arm-crank ergometry is now well established, certain technical limitations remain.¹ It is most difficult to assess blood pressure (BP) by the standard cuff method in an exercising arm. Consequently, BP measurements during arm-crank ergometry are generally obtained by 1 of 2 methods: measuring pressure in an inactive arm while the subject continues cranking with the other or having the subject crank with both arms and pause briefly between stages (i.e., immediately after cessation of exercise).² Unfortunately, both methods have potential drawbacks. High workloads may be difficult to maintain with single arm cranking, whereas the validity of immediate postexercise BP measurements has not been established.

We report an alternative method of assessing systolic BP during arm-crank ergometry, using Doppler flow-meter techniques to measure the difference in ankle pressure at rest and during exercise. We describe our preliminary evaluation of this technique in which we compared estimated values of systolic BP during arm-crank ergometry with those obtained immediately after exercise by the standard cuff method.

METHODS

Subjects: Our study population consisted of 18 untrained healthy men with no evidence of peripheral vascular disease by laboratory evaluation. Their mean ($\pm$ standard deviation) age was 32 ± 7 years, height was 179 ± 5 cm and weight was 81 ± 14 kg.

Arm ergometer testing: Each subject underwent an assessment of upper extremity performance using a cycle ergometer modified for arm cranking, as previously described.³ The ergometer was positioned so that the subject could arm-crank seated upright with feet firmly planted on the floor, adjusted so that the midpoint of the sprocket wheel was at shoulder height. The protocol included a 3-minute initial workload (warm-up) with the subject exercising at $150 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$, using a cranking rate of 60 rpm. Thereafter, the workload was increased in stages by $150 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$ every 3 minutes to attainment of $450 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$.

The exercise electrocardiogram was monitored continuously by telemetry (Mennen Greatbatch) with single-channel (CM_5) recordings made at the end of each exercise stage.

Ankle/brachial systolic blood pressure measurements: Ankle systolic BP was measured at rest with the subject seated upright, at 1-minute intervals during exercise, 15 seconds before completion of each exercise stage and immediately after each workload using a

Doppler stethoscope (Figure 1). The technique involves a pneumatic cuff (standard adult blood pressure cuff) wrapped snugly around the ankle and lower calf (just proximal to the malleoli). The dorsalis pedis artery was located by the Doppler stethoscope and its flow monitored continuously during cuff inflation to suprasystolic pressures, that is, until pulsatile flow ceased. The point at which pulsatile flow resumed during cuff deflation was taken to be ankle systolic BP.

Brachial systolic BPs were determined by a standard sphygmomanometer at rest (seated) and immediately after each exercise workload, simultaneous to the measurement of ankle systolic pressures. All postexercise measurements, whether by Doppler or auscultation, were made with the subject at rest (no longer cranking with either arm), within 15 seconds after completing each exercise stage. Brachial and ankle pressures were measured independently by separate investigators, each blinded to the other's results. To estimate brachial systolic BP during exercise, the following formula was used to correct for the hydrostatic difference between the heart and the ankle: Exercise brachial systolic BP = (resting brachial systolic BP) + (exercise ankle systolic BP - resting ankle systolic BP).

Statistics: Data were compared using the paired *t* test. A *p* value of <0.05 was considered statistically significant. Statistical methods were those as outlined by Steel and Torrie.⁴ Values are expressed as mean $\pm$ standard deviation.

RESULTS

All 18 subjects completed the arm-crank ergometer protocol without demonstrating significant ST-segment depression, serious ventricular arrhythmias, abnormal BP responses or symptoms.

Preexercise resting brachial systolic BP averaged 129 ± 14 mm Hg, whereas simultaneously measured ankle systolic BP was 190 ± 15 mm Hg. At each workload, brachial systolic BP measured immediately after exercise was significantly lower ($p < 0.001$) than the estimated systolic BP calculated from ankle pressure measurements taken just before cessation of exercise. The difference between measured and estimated pressures increased with progressive workloads (Figure 2), corresponding to mean values of 12, 29 and 31 mm Hg at 150, 300 and 450 $\text{kg} \cdot \text{m} \cdot \text{min}^{-1}$, respectively. These differences equalled the average decrease in ankle systolic BP from its maximum value during arm cranking, to its level just after cessation of exercise. Comparative data for the rate-pressure products at these workloads, using both estimated and measured values of systolic BP, are listed in Table I.

DISCUSSION

The product of the heart rate times systolic BP correlates well ($r = 0.92$) with the measured myocardial oxygen consumption.⁵ Patients with exercise-induced ischemia have been shown to develop angina pectoris, significant ST-segment depression, or both, at a reproducible heart rate-systolic BP product, providing evidence for an "ischemic threshold" at which myocardial oxygen demands exceed myocardial oxygen supply.⁶

TABLE I Hemodynamic Responses to Arm Ergometry at Three Progressive Workloads

	Workload ($\text{kg} \cdot \text{m} \cdot \text{min}^{-1}$)		
	150	300	450
Heart rate ($\text{beats} \cdot \text{min}^{-1}$)	101 ± 13	126 ± 19	152 ± 18
Heart rate-systolic BP product ($\text{mm Hg} \times \text{beats} \cdot \text{min}^{-1} \times 10^{-3}$)			
Measured	14 ± 3	18 ± 4	23 ± 3
Estimated	$15 \pm 3^*$	$22 \pm 5^*$	$28 \pm 5^*$

* $p < 0.001$.

Previous studies^{7,8} in cardiac patients have reported a higher heart rate-systolic BP product at the ischemic threshold during arm versus leg exercise. These data suggest that the heart rate-systolic BP product during arm exercise may not reflect myocardial oxygen con-

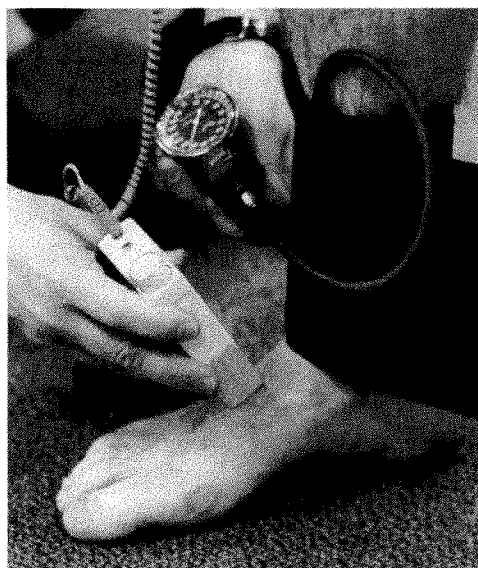


FIGURE 1. Technique for ankle systolic blood pressure measurements using a pneumatic cuff and an ultrasound Doppler stethoscope.

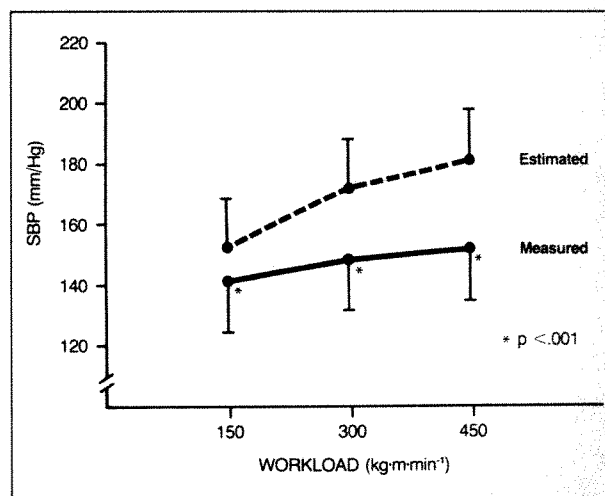


FIGURE 2. Comparison of the postexercise measured and estimated systolic blood pressure for 3 progressive arm-crank ergometer workloads. Values are expressed as mean $\pm$ standard deviation.

sumption as accurately as during leg exercise. Although other determinants of myocardial oxygen consumption, such as myocardial contractility and left ventricular wall stress, have been suggested as variables that may account for the differences in ischemic threshold,² methodologic factors may also be important.

Several lines of evidence suggest that the immediate postexercise systolic BP in a fatigued arm may be considerably lower than maximum arterial blood pressure during arm-crank ergometry. It has been repeatedly shown that in a supine adult with a normal peripheral circulation, the brachial and ankle systolic BPs are equal.^{9,10} Even under conditions of light exercise, the ankle pressure increases in parallel with brachial pressure. This fact has long been used as a diagnostic criterion when evaluating peripheral vascular disease.⁹⁻¹¹

Studies of the lower extremities during and immediately after graded treadmill walking, using a Doppler flowmeter and pneumatic cuff, have shown that there is a brief, transient decrease in ankle systolic BP relative to brachial pressure. This response is presumably related to the decreased vascular resistance within the skeletal muscle.¹² The magnitude and duration of this pressure drop is related to the intensity of the workload; thus, it seems likely that similar responses would occur in the upper extremities after arm-crank ergometry.

To evaluate this question and take advantage of the known ankle to brachial systolic pressure relation, we monitored ankle systolic pressures during arm-crank ergometry. Because our subjects were sitting while cranking and not supine, it was necessary to correct the pressure measurements for the difference in level between the heart and the ankles. This was accomplished by initially measuring both brachial and ankle systolic pressures at rest. During exercise it was possible to measure ankle pressures repeatedly and the increases noted were taken to reflect similar increases in brachial pressures. Thus, true exercising pressures were estimated by adding the increase in ankle pressure to the baseline (resting) brachial pressure measurement. Figure 2 shows these estimates for the 3 different workloads at a time just before cessation (within 15 seconds) of exercise, and compares them to brachial pressures measured as quickly as possible after completion of exercise.

The differences noted support the hypothesis that brachial pressures measured after exercise do not accurately reflect true systemic pressures during arm-crank ergometry. It is unlikely that progressive isometric ac-

tivity of the leg and foot muscles may have elevated pedal pressures and overestimated "true" systemic pressures, since ankle pressures increased proportionately with exercise. The data show a significant decrease in systolic pressure immediately after exercise, the magnitude of which is related to the workload. This response may reflect a decrease in cardiac output secondary to a reduction in venous return, decreased vascular resistance,¹² or both.

The technique of ankle pressure measurement is valid and reproducible only for patients with a normal peripheral arterial system.^{9,10,13} The presence of lower extremity atherosclerotic occlusive disease, found in a significant number of patients with coronary artery disease,^{14,15} changes the relation between ankle and brachial systolic pressures and renders the corrections described above invalid.

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Hemodynamic Effects of Oral Nicorandil in Congestive Heart Failure

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Twenty-five patients with congestive heart failure (CHF) underwent a double-blind randomized study of the acute hemodynamic effects of orally administered nicorandil, a newly developed vasodilator drug. A dose range of 10 to 60 mg was studied. Nicorandil, at a dose of 60 mg, caused statistically significant decreases in systemic systolic and diastolic blood pressure, right atrial pressure, pulmonary capillary wedge pressure, systemic and pulmonary vascular resistance and systolic and diastolic pulmonary arterial pressure. A brief increase in cardiac index attributable to an increase in stroke volume without a change in heart rate was also observed. A dose of 40 mg produced similar results in cardiac index and systemic and pulmonary vascular resistance, but changes in other hemodynamic parameters were much smaller in magnitude and usually not of statistical significance. No significant hemodynamic response was seen to doses of 10 and 20 mg of nicorandil. Duration of action was short with nearly all hemodynamic parameters returning close to baseline within 3 hours. This rapid decrease in activity occurred in concert with a rapid plasma clearance of nicorandil as determined by serial measurements of plasma drug concentration. This study suggests that first-dose orally administered nicorandil elicits favorable, but brief, hemodynamic effects in CHF at doses ≥ 40 mg.

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Nicorandil, a nicotinamide derivative, is a recently developed vasodilator drug with potent coronary and peripheral vascular activity.¹ Hemodynamic studies in animals, normal volunteers and patients with ischemic heart disease have shown that nicorandil can decrease systemic blood pressure, peripheral vascular resistance, left ventricular end-diastolic pressure and pulmonary arterial pressure, and increase cardiac output and coronary blood flow.²⁻⁴ Such a pharmacologic profile would predictably be of benefit to patients with congestive heart failure (CHF). The results of a preliminary nonblinded and noncontrolled study involving 11 CHF patients indicated that nicorandil may favorably alter hemodynamics (decrease of vascular resistances and ventricular filling pressures) in this clinical setting.⁵ This study was performed using a double-blind, placebo-controlled design to investigate the acute hemodynamic responses to single oral doses of nicorandil over a broad dose range in patients with CHF.

METHODS

Patient population: Twenty-five patients (22 men, 3 women, mean age 51 years, range 25 to 74) with CHF were studied. Two patients were classified as New York Heart Association functional class I, 10 as functional class II, 10 as functional class III and 3 as functional class IV. The 2 patients classified as functional class I had dyspnea only with at least moderate or more exertion, but were included because each had other indicators of CHF; each had jugular venous distention, an S₃ gallop, cardiomegaly, hepatomegaly, depressed ejection fractions (10 and 15%) and elevated filling pressures (≥ 25 mm Hg). All patients had undergone diagnostic cardiac catheterization; 12 patients had ischemic cardiomyopathy, 12 had idiopathic dilated cardiomyopathy and 1 had alcoholic cardiomyopathy. Left ventricular ejection fractions ranged from 10 to 36%. Angiotensin-converting enzyme inhibitors were withdrawn ≥ 48 hours before initiation of the study. Digitalis, diuretics, nitrates and all other vasodilators were withheld ≥ 12 hours before the study.

Protocol: The protocol was approved by the Institutional Human Subjects Research Review Committee and each patient gave written informed consent.

Randomization to either placebo or nicorandil was done on the day of dosing in a manner that blinded the patients, nurse technicians and investigators. A block design was used such that each dose level was completed and its safety affirmed before incrementing to the

TABLE I Pretreatment Baseline Values

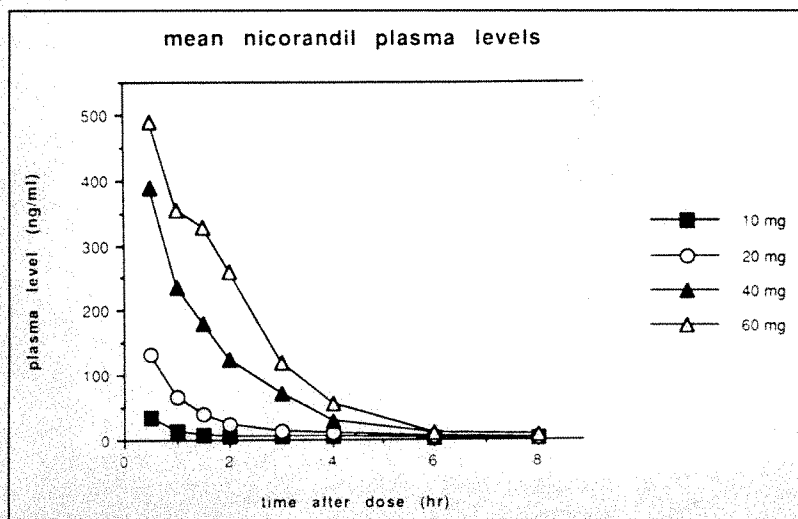
	Placebo	Nicorandil Dose Level (mg)			
		10	20	40	60
Cardiac index (liters/min/m ²)	1.85 ± 0.56	1.88 ± 0.43	2.06 ± 0.51	1.91 ± 0.41	1.90 ± 0.56
Stroke volume index (ml/systole/m ²)	24 ± 11	21 ± 5	23 ± 7	22 ± 3	19 ± 7
Heart rate (systoles/min)	84 ± 16	92 ± 17	91 ± 12	86 ± 16	99 ± 12
Systolic arterial pressure (mm Hg)	109 ± 5	119 ± 22	132 ± 32	116 ± 10	120 ± 12
Diastolic arterial pressure (mm Hg)	80 ± 7	80 ± 9	86 ± 20	79 ± 14	87 ± 9
Total SVR (dynes s cm ⁻⁵)	2,043 ± 614	2,219 ± 719	2,173 ± 763	2,253 ± 610	2,361 ± 865
SAR (dynes s cm ⁻⁵)	1,789 ± 491	1,891 ± 536	2,015 ± 738	1,950 ± 509	2,027 ± 690
Pulmonary systolic pressure (mm Hg)	51 ± 11	62 ± 7	56 ± 26	50 ± 11	56 ± 10
Pulmonary diastolic pressure (mm Hg)	26 ± 8	26 ± 4	27 ± 9	24 ± 6	31 ± 7
Total PVR (dynes s cm ⁻⁵)	821 ± 402	911 ± 303	863 ± 411	865 ± 296	988 ± 457
PAR (dynes s cm ⁻⁵)	213 ± 143	319 ± 116	313 ± 175	311 ± 175	330 ± 101
PCWP (mm Hg)	25 ± 8	24 ± 4	26 ± 11	23 ± 6	26 ± 8
Right atrial pressure (mm Hg)	11 ± 4	13 ± 6	8 ± 4	12 ± 5	13 ± 7

All values are mean ± standard deviation.
 PAR = pulmonary arteriolar resistance; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SAR = systemic arteriolar resistance; SVR = systemic vascular resistance.

next level. Doses were given as follows: within level 1, 5 patients received 10 mg nicorandil randomized with 2 patients receiving identical-appearing placebo; at level 2, 5 patients received 20 mg nicorandil and 1 patient placebo; at level 3, 5 patients received 40 mg nicorandil and 1 patient placebo; and at level 4, 5 patients received 60 mg nicorandil and 1 patient placebo. Mixed venous blood was drawn (via distal port of the pulmonary artery catheter) for measurement of plasma nicorandil concentration at 0, 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours after administration of the study drug. Central hemodynamic measurements were obtained with patients in the supine position at 45, 30 and 15 minutes before dosing (and averaged for baseline), and at 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours after the study drug was administered. After supine measurements over the interval between 15 minutes before dosing and 4 hours after dosing, patients

were placed in a standing position for 5 minutes and upright hemodynamic parameters were recorded. Fasting was maintained for a period lasting from 8 hours before dosing until 4 hours after the study drug was given, after which a standard light snack was allowed.

Procedures: On the day before initiation of the study, a triple lumen, flow-directed thermodilution catheter was placed percutaneously in the pulmonary artery. This catheter was interfaced with Spacelabs 90303A pressure amplifiers and 90409 recording systems (Spacelabs). Cardiac output measurements were initiated at end-expiration and performed in triplicate to obtain an average value; calculations were obtained using a COM1 computer (American Edwards Laboratory). Systemic blood pressure was measured with an inflatable cuff and mercury column sphygmomanometer. Heart rate and rhythm were continuously monitored.

**FIGURE 1.** Plasma concentrations of nicorandil after oral administration of a single dose.

The plasma samples were stored at -20°C until assays could be performed by the drug metabolism research unit at The Upjohn Company. The samples were analyzed by gas chromatography/mass spectrometry.

Statistical analysis: The hemodynamic data were analyzed with Dunnett's multiple comparison test, using the average baseline measure as the control. An overall, 2-factor repeated measures analysis of variance was done to obtain the appropriate error term for the Dunnett tests. Log transformations (base e) were done for some of the hemodynamic measurements in order to make the variances among dose levels more homoge-

nous. Statistical significance was accepted at the 95% confidence level ($p < 0.05$).

RESULTS

Nicorandil was rapidly absorbed (Figure 1). A linear correlation ($r = 0.98$; $p < 0.01$) was found between the nicorandil dose and the plasma level at 30 minutes. Elimination was quite rapid with the half-life ranging between 1 and 2 hours over the dose range of 20 to 60 mg.

Baseline hemodynamic parameters for each treatment group are listed in Table I and drug-induced

FIGURE 2. Changes from baseline in cardiac index, stroke volume and heart rate after oral administration of increasing doses of nicorandil. Values are expressed as mean $\pm$ standard error of the mean.

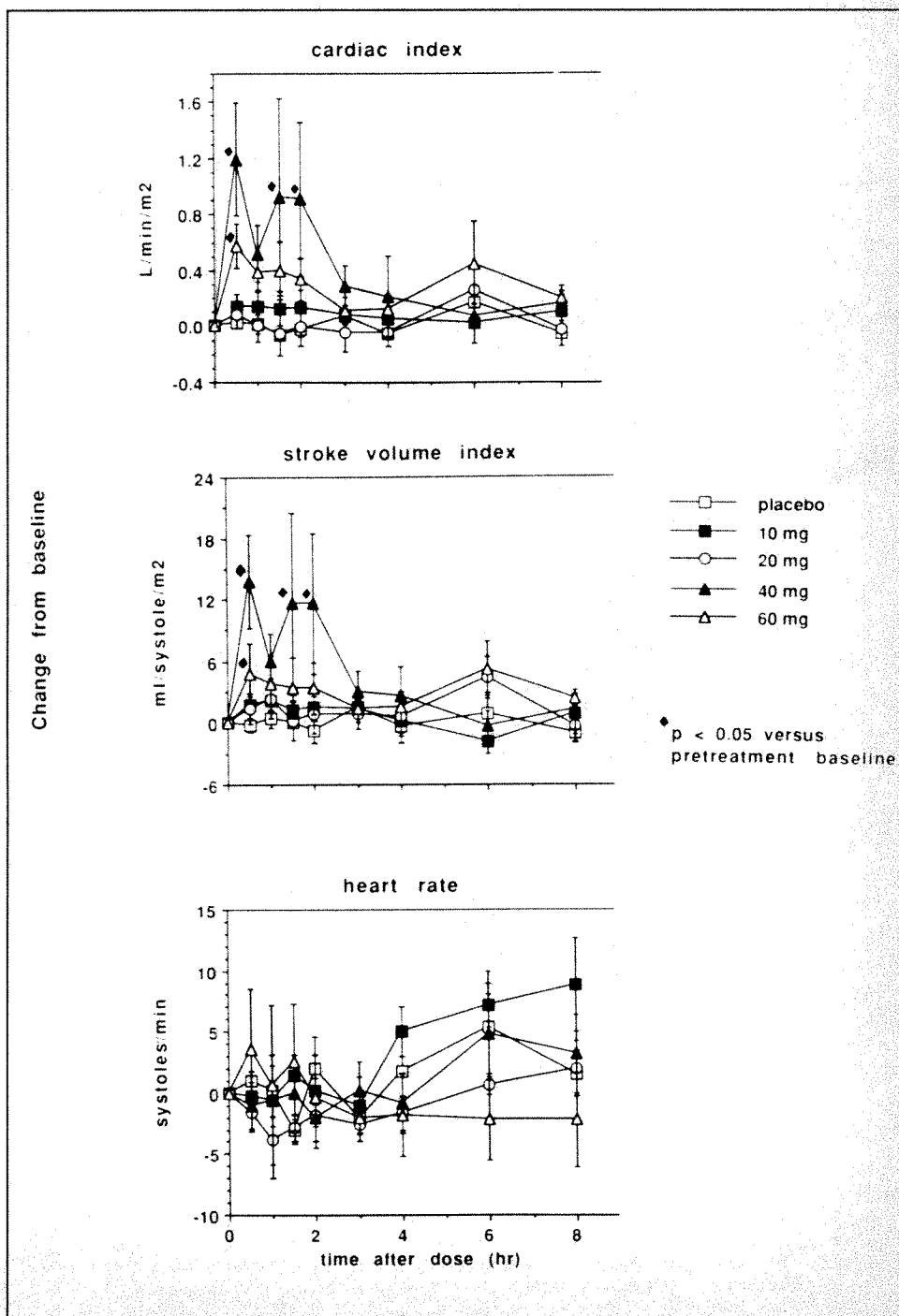


TABLE II Supine Versus Standing Pretreatment Baseline Values

	Supine	Standing
Cardiac index (liters/min/m ²)	1.93 ± 0.43	1.87 ± 0.37
Stroke volume index (ml/systole/m ²)	22 ± 7	20 ± 6*
Heart rate (systoles/min)	90 ± 15	98 ± 16†
Systolic arterial pressure (mm Hg)	119 ± 19	120 ± 19
Diastolic arterial pressure (mm Hg)	83 ± 12	85 ± 13
Total SVR (dynes s cm ⁻⁵)	2,163 ± 589	2,272 ± 638
SAR (dynes s cm ⁻⁵)	1,895 ± 507	2,178 ± 607†
Pulmonary systolic pressure (mm Hg)	55 ± 15	40 ± 15†
Pulmonary diastolic pressure (mm Hg)	27 ± 7	20 ± 8†
Total PVR (dynes s cm ⁻⁵)	864 ± 317	651 ± 289†
PAR (dynes s cm ⁻⁵)	284 ± 131	282 ± 136
PCWP (mm Hg)	24 ± 7	15 ± 8†
Right atrial pressure (mm Hg)	11 ± 5	4 ± 4†

All values are mean ± standard deviation.
* p < 0.05 versus supine value; † p < 0.001 versus supine value.
Abbreviations as in Table I.

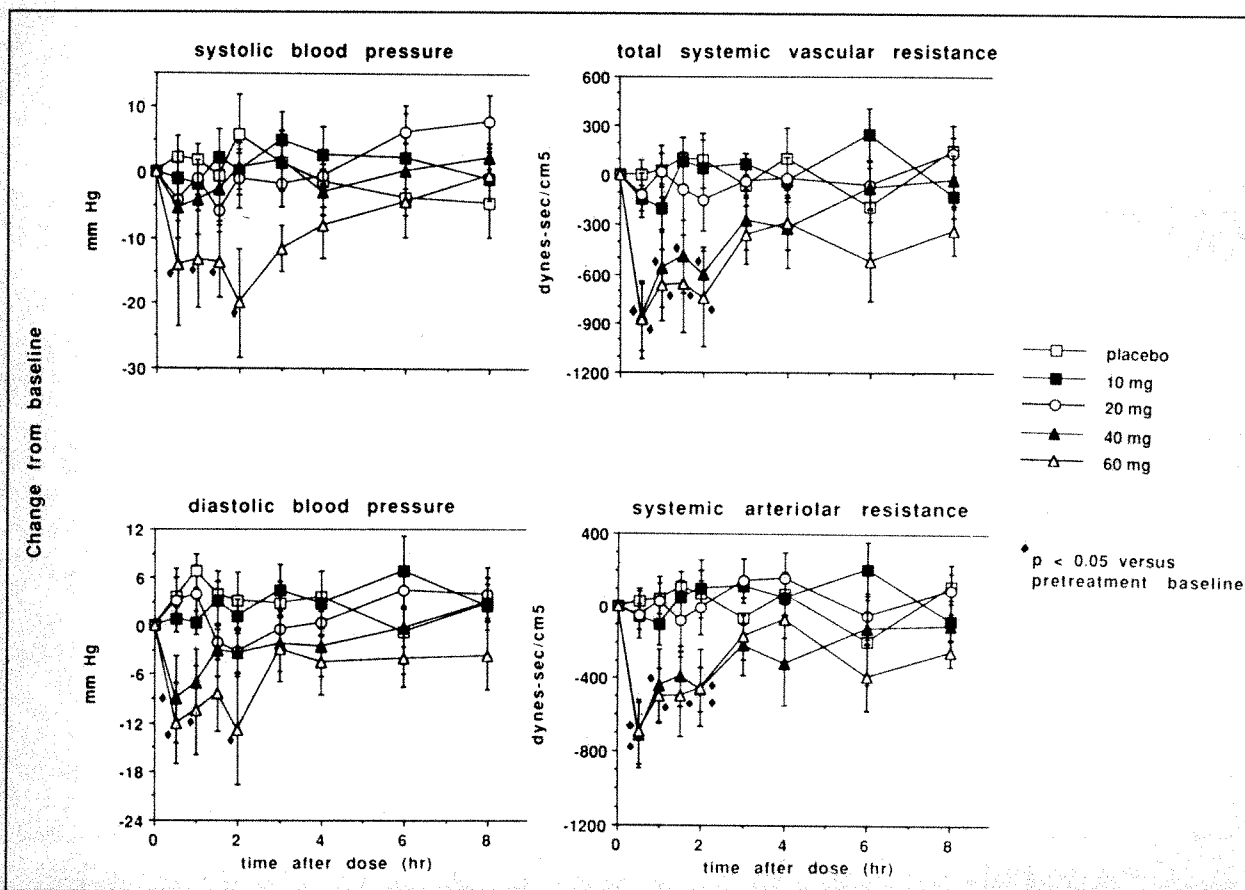
changes are shown in Figures 2, 3, 4 and 5. Nicorandil at 40 and 60 mg increased cardiac index 63 and 32%, respectively, at 30 minutes (Figure 2). This response statistically returned to baseline by ≤3 hours after dosing. The amplitude and persistence of response beyond 30 minutes in the 40 mg group were attributable to a rather dramatic response by 1 individual. Augmentation of cardiac output was secondary to an increase in stroke

volume, as heart rate did not significantly change at any dose level (Figure 2).

Systemic blood pressure was significantly decreased only with 60 mg of nicorandil (Figure 3). A downward trend was also noted with 40 mg, but was statistically significant only at 30 minutes (Figure 3). Total systemic vascular resistance decreased 38 and 37%, respectively, 30 minutes after 40 and 60 mg nicorandil (Figure 3). The significant changes in systemic and pulmonary pressures and vascular resistances lasted ≤3 hours. Pulmonary artery pressures were significantly decreased only by 60 mg of nicorandil, although both the 40 and 60 mg doses decreased total pulmonary vascular resistance (Figure 4).

Nicorandil at 60 mg significantly decreased pulmonary capillary wedge pressure for ≤2 hours (Figure 5). A smaller decrease was observed after 40 mg. Nicorandil at 60 mg decreased mean right atrial pressure for ≤3 hours (Figure 5).

Statistically significant hemodynamic changes occurred at predrug baseline when the patients assumed the standing position; these data are listed in Table II. Comparison of the upright and supine response curves to nicorandil showed that body position had a negligible effect on the hemodynamic activity of this drug. The direction and amplitude of all hemodynamic parameters changed similarly in both positions relative to their own

**FIGURE 3.** Changes from baseline in systemic blood pressure and vascular resistance after oral administration of nicorandil in a heart failure population. Values are expressed as mean ± standard error of the mean.

predrug baselines. Although nicorandil was generally well tolerated, 1 patient did develop symptomatic orthostatic hypotension 30 minutes after a 60 mg dose.

The direction and amplitude of the hemodynamic responses to nicorandil were not related to baseline functional classification, overall clinical status or etiology (ischemic versus nonischemic cardiomyopathy) in this heart failure population.

DISCUSSION

Hemodynamic effects: Nicorandil at 60 mg elicited statistically significant hemodynamic changes consistent with the arterial and venous vasodilating properties of this agent. The responses to 40 mg generally were less in magnitude and/or shorter in duration. An increase in cardiac index was observed with both 40 and 60 mg. However, much of the 40 mg increment was attributable to an impressive response (100% increase) by 1 patient. It is unclear why this individual exhibited such a dramatic response, as he did not clearly differ demographically or hemodynamically at baseline from other patients in the study. His cardiac output returned to baseline within 4 hours, suggesting that the increase was drug-related. Dosages of 10 and 20 mg did not produce any important central hemodynamic effects.

Patients with nonfailing ischemic heart disease often experience symptomatic hypotension after a 40 mg dose; 20 mg has been suggested as the optimal dose for

antianginal activity.^{4,6} Sixty mg of nicorandil was required to produce consistent hemodynamic effects in our heart failure population. Relative resistance to vasodilator stimuli in CHF patients has been previously established.⁷ The duration of action of nicorandil was quite short, with return of nearly all hemodynamic parameters to near baseline within 3 hours. The loss of hemodynamic activity in this study appeared to correspond closely with the rapid decrease in plasma concentrations of nicorandil (Figure 1).

The acute hemodynamic response to a vasodilator in heart failure does not predict effectiveness as long-term therapy.⁸ Hemodynamic tolerance to nicorandil does not appear to occur in animal models.⁹ However, this issue has yet to be examined in human subjects. Nicorandil appears to evoke vasodilation of arterial and venous vasculature. Long-term decrease of systemic vascular resistance alone usually fails to improve clinical status and exercise capacity in CHF patients, despite concomitant enhancement of stroke volume and cardiac output.¹⁰⁻¹² Although no single hemodynamic parameter has yet been identified as a predictor of the clinical efficacy of a drug, several studies suggest that a decrease of pulmonary capillary wedge pressure, pulmonary vascular resistance and right-sided heart filling pressure are important in improving exercise capacity in CHF patients¹³⁻¹⁶; first-dose nicorandil at ≥ 40 mg decreases these hemodynamic parameters. Long-term

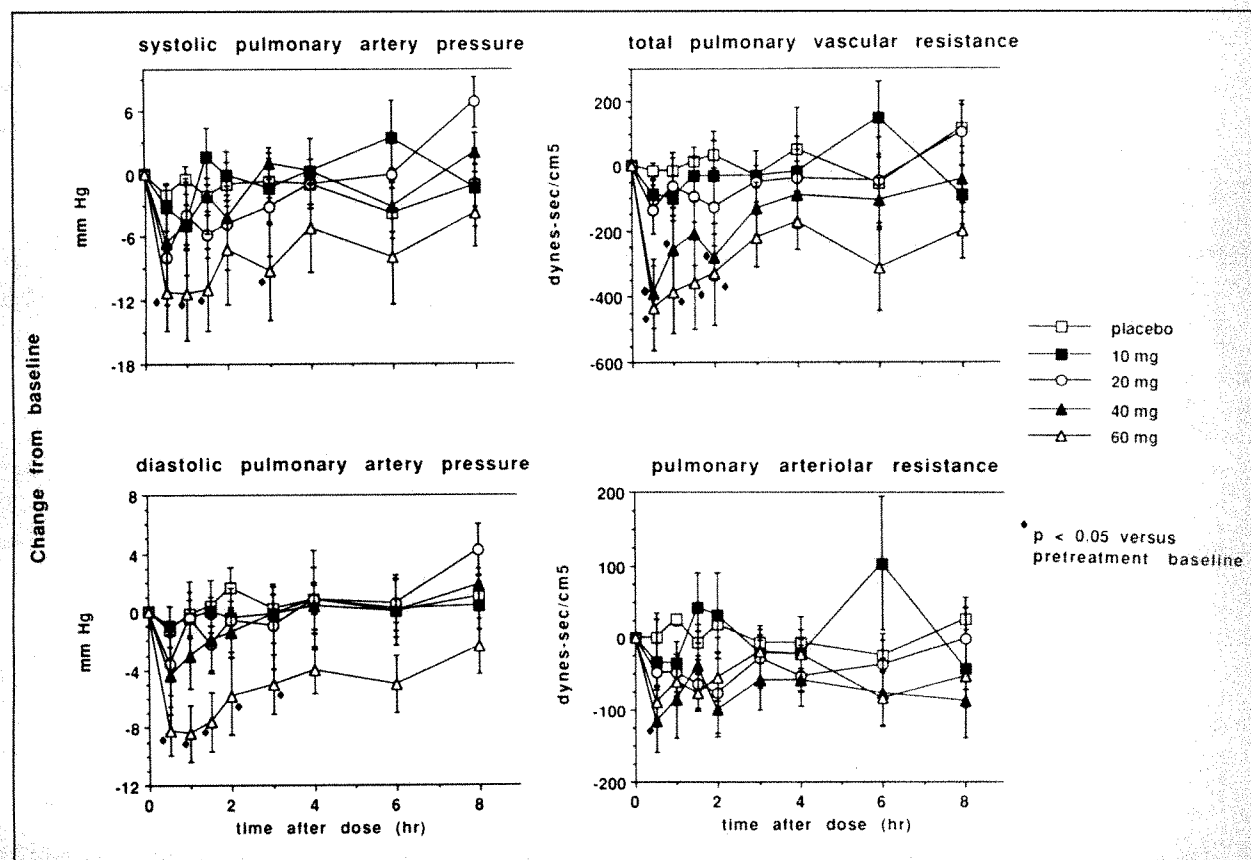


FIGURE 4. Changes from baseline in pulmonary arterial pressures and vascular resistance after increasing doses of nicorandil. Values are expressed as mean $\pm$ standard error of the mean.

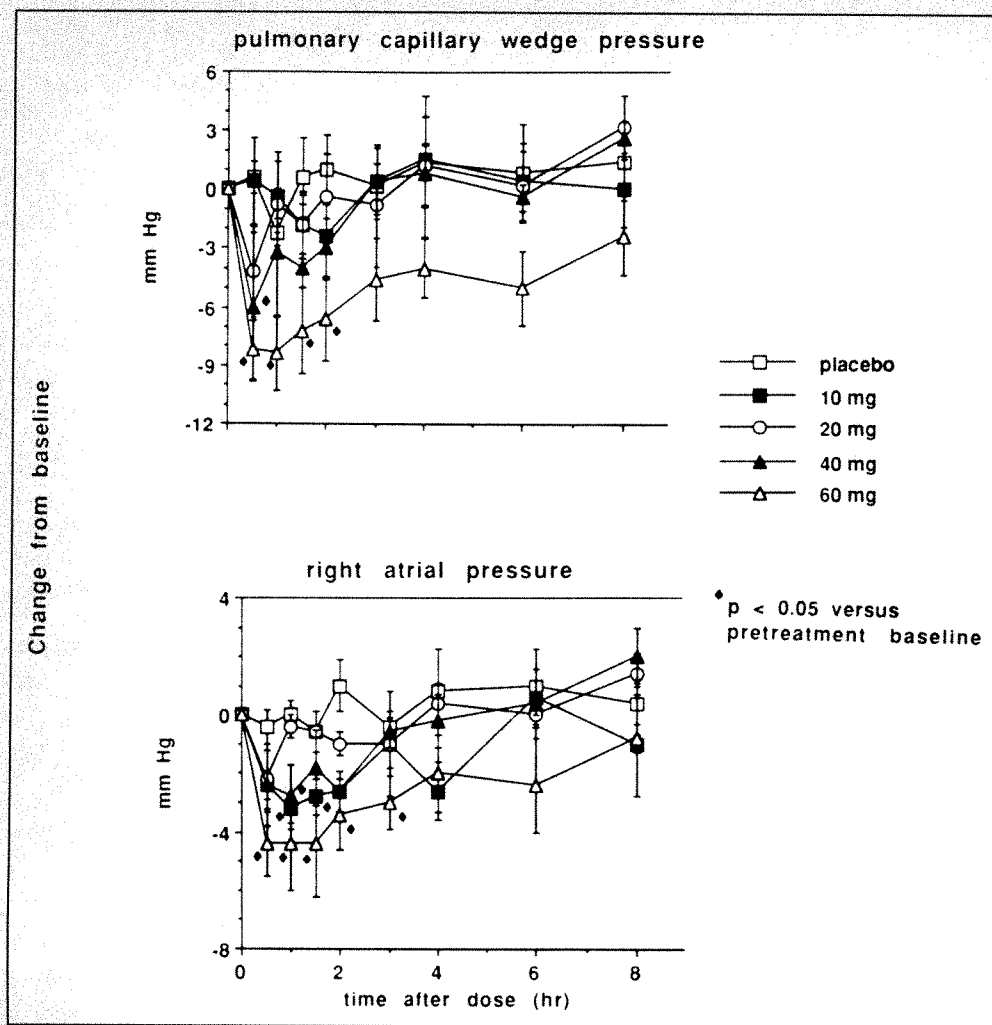


FIGURE 5. Changes from baseline in pulmonary capillary wedge pressure and right atrial pressure after oral nicorandil administration in a heart failure population. Values are expressed as mean $\pm$ standard error of the mean.

studies in chronic CHF will be necessary to determine whether nicorandil can be of benefit to patients in this clinical setting.

Study design: The study design itself deserves comment. The investigators generated the design to simultaneously address several unknown questions about the oral administration of nicorandil in chronic CHF. These include the following: what is the hemodynamically ineffective dose range; the minimal effective dose; recommended starting dose; effective dose range; duration of effect (at each dose); and the relation of the dose to plasma level and hemodynamic effect? A block design, started at low doses with 1 or 2 blinded placebo treatments at each level, was used to address the issues of effectiveness and safety of each dose before advancing to the next level. The investigators believe that the study design used effectively and convincingly addressed the aforementioned questions and the objectives of the investigation.

Limitations of the study: A total of 5 subjects for each treatment group might be viewed as a major limitation of this study. However, the data of 25 subjects in 5 increasing dose groups suggest that increasing the number of subjects in each group would not likely

change the results substantially or the interpretation of such.

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Saline Contrast Enhancement of Tricuspid Regurgitant Jets Detected by Doppler Color Flow Imaging

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Contrast techniques have been used to improve detection of peak velocities by Doppler spectral analysis. To define the effect of contrast enhancement on the tricuspid regurgitation (TR) jet area and length, 29 patients were studied (25 transthoracic, 4 transesophageal) with 2-dimensional color flow imaging. Three- to 5-ml of agitated saline was injected and images were obtained from 4-chamber views at 12- or 16-cm depth setting. Color gain was optimized to display TR jet at baseline and then reduced to minimal settings before injection. Measurements of TR jet area and length were made in 3 to 5 consecutive cycles. A ratio of TR jet area to 2-dimensional area was derived. TR jet area at baseline was 4.7 ± 3.6 cm² and increased significantly ($p < 0.0001$) in 26 patients to 8.1 ± 6.3 cm² after contrast enhancement. Jet length at baseline was 3.4 ± 1.7 cm and increased significantly ($p < 0.0001$) in 20 patients to 4.1 ± 1.8 cm after contrast enhancement. The ratio of TR jet area to right atrial area also increased significantly ($p < 0.0001$) to >0.20 in 18 of 28 patients after enhancement. Increases in jet area and length were not associated with changes in TR jet or diastolic inflow velocities measured by continuous wave Doppler at baseline and after contrast. Thus, contrast enhancement increases the amplitude of Doppler signals responsible for transvalvular and regurgitant flow. By reducing the effect of attenuation and improving signal-to-noise ratio, it improves delineation of the TR jet using color flow imaging.

(Am J Cardiol 1990;65:1368-1371)

Doppler color flow imaging provides real-time visualization of the spatial distribution of the systolic flow disturbance of tricuspid regurgitation (TR). It allows quantification of jet width, length and area (relative to right atrial size) and may better reflect the severity of TR compared to right ventricular angiography.^{1,2} Jet boundary definition can be difficult in certain patients, however, due to technical limitations such as attenuation caused by the depth of the flow disturbance, limited display of low velocities, limitations in gain, axial or lateral resolution and spatial filtering of the imaging system.³ Previous investigators have reported on the use of contrast enhancement of ultrasonic signals displayed by M-mode, 2-dimensional echocardiography, pulsed and, recently, continuous wave Doppler techniques to detect TR.⁴⁻⁸ We report our use of peripheral intravenous saline injections in patients to enhance the visualization of TR jets by color flow imaging. We also define the factors responsible for improved detection of the TR jet and its implications for semi-quantitative estimation of the severity of regurgitant jets in general by Doppler color flow imaging.

METHODS

Seventeen men and 12 women, whose ages ranged from 32 to 83 years, were studied. In 25 patients standard transthoracic 2-dimensional echocardiograms and Doppler color flow images were obtained with a Hewlett-Packard 77020A ultrasound system using a 2.5-MHz transducer. We used the apical 4-chamber view to assess TR by color flow imaging and to measure right atrial area by planimetry (average of 3 measurements from still-frames at midsystole). We used continuous wave Doppler to measure the peak tricuspid inflow velocity and the TR jet velocity. In another 4 patients transesophageal echocardiography with color flow imaging was performed with a 5-MHz transducer. A 4-chamber plane was also used for assessment of TR and measurement of right atrial area.

Color flow imaging of the TR was obtained before contrast enhancement in all patients. Color gain was adjusted to display the jet envelope optimally, resulting in a minimum of background noise. Measurement of maximal jet area (cm²) and jet length (cm) was performed in at least 3 still-frame images and averaged (Figure 1). Mild TR was defined as a jet area <4 cm², moderate TR as 4 to 8 cm² and severe TR as >8 cm². The ratio of TR jet area to right atrial area was also determined and defined as mild if <0.20 , moderate if 0.20 to 0.40 and severe if ≥ 0.40 .

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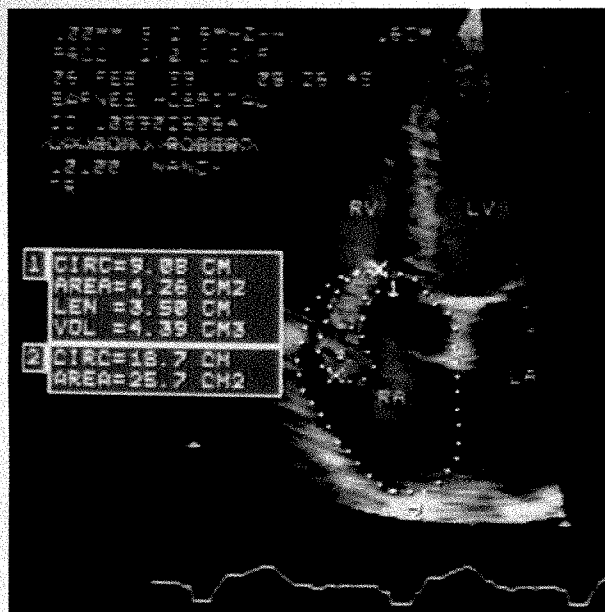


FIGURE 1. Transthoracic apical 4-chamber view of the tricuspid regurgitant jet at baseline. Jet area (4.26 cm²) and length (3.50 cm) are displayed (1) compared to right atrial area (2) of 25.7 cm². LA = left atrium; RA = right atrium; RV = right ventricle.

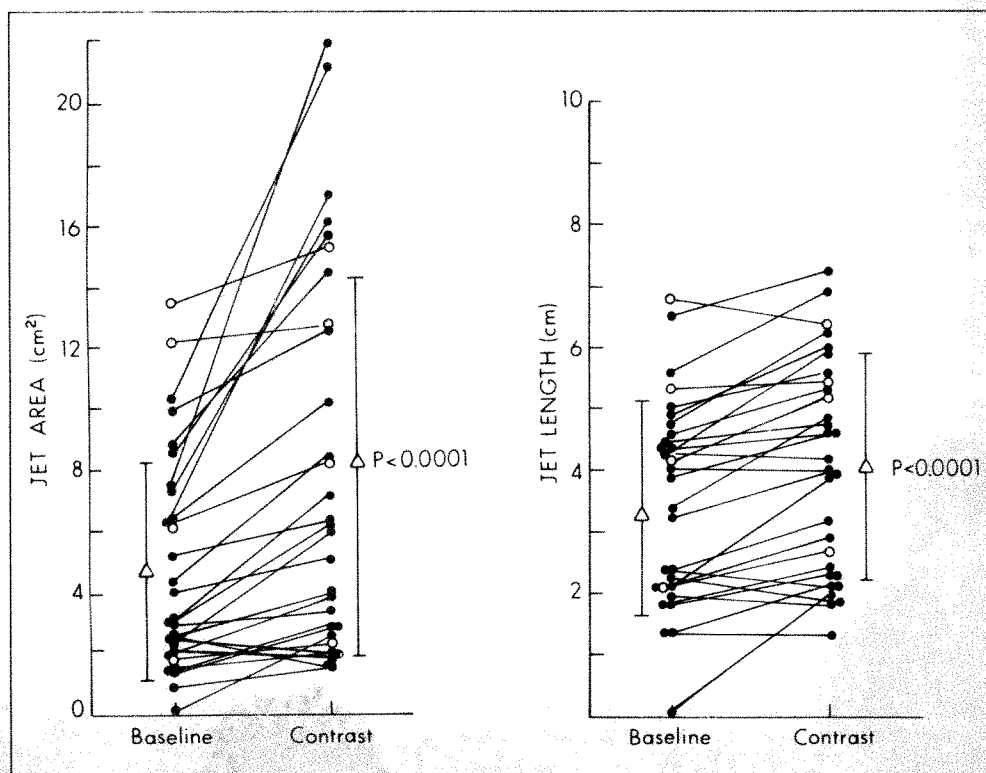


FIGURE 2. Transthoracic apical 4-chamber view of the contrast-enhanced jet of the same patient as in Figure 1. Note increase in jet area (10.3 cm²) and length (4.45 cm). LV = left ventricle; other abbreviations as in Figure 1.

Contrast enhancement was accomplished with injections of normal saline (3 to 5 ml) via the antecubital vein or directly into a proximal port of a Swan-Ganz catheter with at least 2 injections per patient. A 3-way stopcock was connected to the intravenous line and two 10-ml syringes were attached to each port of the stopcock. Normal saline was agitated for at least 10 seconds between the 2 syringes (air introduced into 1 syringe

before agitation). After the visible air was expelled, forceful hand injection of saline was performed with simultaneous color flow imaging or continuous wave Doppler recording of the TR jet and recorded on ½ inch videotape. The continuous wave Doppler TR jet velocity and the peak diastolic transtricuspid velocity was measured in 22 patients. In addition, 7 patients had continuous wave Doppler TR jets measured at baseline condi-

FIGURE 3. Individual values at baseline and after contrast enhancement for tricuspid regurgitant jet area and jet length. Closed circles are transthoracic and open circles are transesophageal studies. Group mean $\pm$ 1 standard deviation values are shown as triangles.



tions and after enhancement. Contrast enhancement of continuous wave Doppler signals usually required injections of <3 ml of agitated saline. The Doppler receiver gain and transmit power in the system usually had to be decreased to minimal levels with the injection of saline due to signal saturation. Therefore, color gain was also reduced to the lowest setting before saline injections for measurements of the TR jet after enhancement (Figure 2). Statistical analysis was performed comparing the TR jet length, area and jet to right atrial area before and after contrast injection using a Student's paired *t* test; significance was determined at the $p < 0.05$ level.

RESULTS

Two-dimensional areas, pulsed and continuous wave Doppler: It was possible to measure the right atrial area using transthoracic or transesophageal echocardiography in 4-chamber views in 28 of 29 patients. It ranged from 12.0 to 49.4 cm² (mean $\pm$ standard deviation throughout) 22.5 ± 8.8). Only 17 patients (61%) had a right atrial area >20 cm² (upper limit of normal 19.5).⁹ Continuous wave Doppler measurement of jet velocity was obtained in 22 of 29 patients, 7 of whom were measured only after contrast enhancement. The peak regurgitant jet velocity ranged from 2 to 5.3 m/s (mean 2.91 ± 0.7) and 11 of 22 patients exhibited a jet velocity >3.0 m/s. There was no correlation between continuous wave-measured TR jet velocity and TR jet area or length using color flow imaging, with or without contrast enhancement. Also, no changes were noted in

the TR jet peak velocity or peak diastolic tricuspid inflow velocity in the 7 patients with TR jets in whom measurements were obtained both at control and after contrast enhancement.

Color flow imaging before and after contrast: All patients had enhanced color intensity of the diastolic transvalvular flow in the right atrium and right ventricle after contrast injection. During systole, this resulted in an increase in regurgitant jet area in 24 patients; in 2 patients the color flow area changed minimally and in 3 patients it decreased slightly (Figure 3). The TR area at control ranged from 0 to 13.4 cm² (mean 4.7 ± 3.6). In 13 of 28 patients the TR jet area was >4 cm²; 6 had an area >8 cm². After contrast enhancement the jet area ranged from 1.6 to 21.8 cm² (mean 8.1 ± 6.3) and was significantly increased from control values ($p < 0.0001$); the jet area was >4 cm² in 18 of 29 patients, 12 of whom had areas >8 cm².

Jet length measurements: The TR jet length also increased significantly from control values with contrast enhancement (Figure 3). Jet length at control ranged from 0 to 6.8 cm (mean 3.4 ± 1.7) and 13 of 28 patients had a jet length >4 cm. With contrast enhancement jet length increased significantly ($p < 0.0001$) and ranged from 1.3 to 7.3 cm (mean 4.1 ± 1.8); it increased in 20 patients, did not change or changed minimally in 5 and decreased in 4. After contrast enhancement 15 of 29 patients had a jet length >4 cm.

Ratio of tricuspid regurgitation jet area to right atrial area: The ratio of TR jet area to right atrial area ranged from 0 to 0.60 (mean 0.20 ± 0.15); 11 of 28 patients had a ratio >0.20 . Not surprisingly, the ratio increased significantly with contrast ($p < 0.0001$) and ranged from 0.09 to 0.74 (mean 0.34 ± 0.21); 18 of 28 patients had a ratio >0.20 . An increase in the ratio was seen in 23 patients. In 2 patients it showed little change and decreased in 3 (Figure 4).

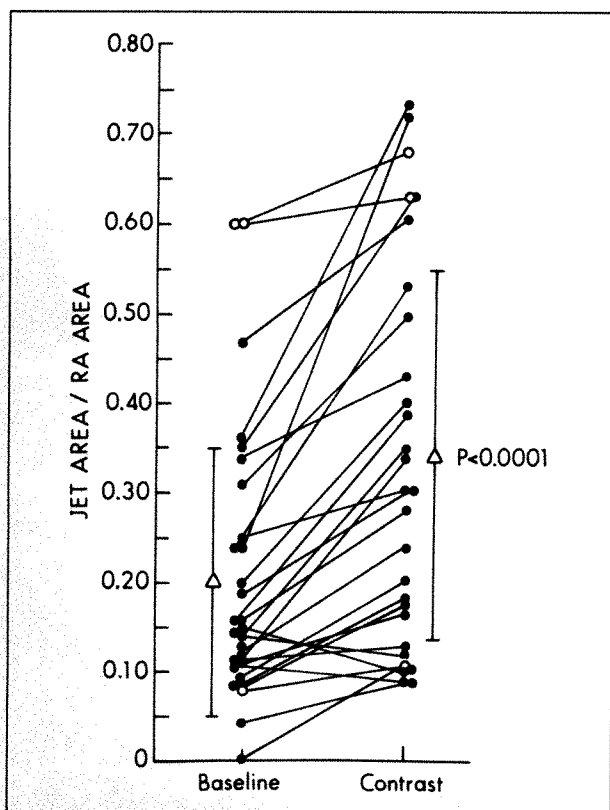


FIGURE 4. Individual values at baseline and after contrast enhancement for the ratio of tricuspid regurgitant jet area to right atrial area. Symbols as in Figure 3.

DISCUSSION

Contrast echocardiography was extensively used before the availability of color flow imaging to evaluate TR using M-mode or 2-dimensional imaging modalities.^{4,5} Many investigators have also used saline contrast injections to enhance the recording of continuous wave Doppler spectra of pulmonary stenosis and TR jets when the jet velocity envelope is not optimally displayed at baseline conditions.⁶⁻⁸ Recently, Becher and Schlieff¹⁰ reported the use of a new contrast agent (SHU-454) to enhance Doppler color flow imaging of the normal diastolic right atrial and right ventricular flow in control subjects. In the present study, we sought to define the role of intravenous injection of normal saline to enhance TR jets in patients. We also wanted to determine its implications in the semiquantitative assessment of the severity of regurgitant lesions in general using color flow imaging.

We used criteria similar to previous studies^{2,11} to define the severity of TR based on the regurgitant area and the ratio of jet area to right atrial area. The relation between the severity of TR and continuous wave-determined jet velocity had not been previously defined. In

our study there was no significant correlation between TR jet area or length and TR velocity. Moreover, no correlation was observed between TR velocity and the ratio of jet area to right atrial area at baseline or after contrast enhancement. Contrast enhancement was associated with increases in jet area in 26 (90%) patients and resulted in a change of the grade of severity in 11 patients (38%). The ratio of jet area to right atrial area also increased by 1 grade of severity in 14 (50%) patients.

The effect of contrast enhancement on TR jet area could have important implications for judging severity of regurgitant lesions by color flow imaging techniques. Previous investigators^{2,11} reported discrepancies between pulsed Doppler or color flow imaging grading of TR jet area and ventriculography. Our results demonstrate that many patients exhibit greater jet area with contrast enhancement. This suggests that the extent of TR may be underestimated by standard transthoracic color flow imaging. It may be due to the depth at which color flow imaging of right atrial flow is performed since depth settings are often >12 cm in standard apical 4-chamber views. We propose that contrast enhancement of TR jets might improve the correlation between color flow imaging and ventriculography, although this requires further validation in studies where the TR volume can be accurately controlled. We noted that increases in TR jet areas with saline contrast enhancement appeared to be less pronounced with transesophageal echocardiography, although only 4 patients were so studied. Our observation seems to support the effect of depth on color flow-imaged TR jet area because the right atrium is closer to the transesophageal transducer, thereby decreasing ultrasonic attenuation despite the higher frequency.

Limitations: We are aware that contrast enhancement could artifactually result in increased blood flow velocities and lead to an enhanced regurgitant color flow map. Initial reports suggested that microbubbles did not travel at a similar velocity as red blood cells.¹² However, recent studies have shown that red blood cell and microbubble velocities are, in fact, the same.¹³ Our results demonstrate that increases in TR jet area observed with color flow imaging and contrast enhancement are not due to increases in velocity of regurgitant flow or transvalvular flow.

Another potential limitation relates to the marked increase in the received signal amplitude of Doppler shifts with contrast enhancement.¹⁰ We minimized this effect with the injection of small amounts of saline and

reduction of the signal or color gain controls as necessary to display the jets without receiver overload or saturation. We did not change maps or filtering settings but, nevertheless, the effect of gain cannot be quantitatively measured in clinical imaging systems. It is possible that results of other clinical studies using different contrast agents or different ultrasound imaging systems may differ. Simpson et al¹⁴ have shown that jet lengths and area may vary depending on the system used, even in the in vitro flow models with controlled settings of flow rates and flow volumes. Further investigation of color flow imaging of TR jets with contrast enhancement is warranted using in vitro systems with controlled amounts of saline injections to measure the effect of regurgitant volume.

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Preoperative Left and Right Ventricular Performance in Combined Aortic and Mitral Regurgitation and Comparison with Isolated Aortic or Mitral Regurgitation

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Left and right ventricular performance characteristics in operative candidates with combined aortic and mitral regurgitation (AR/MR) have not been well defined. Therefore, we determined radionuclide cineangiographic ejection fractions, as well as echocardiographic and hemodynamic parameters, in 8 symptomatic patients undergoing double-valve replacement with pure, severe AR/MR. In order to gain insight into the basis for the poor postoperative survival in patients with this intrinsically bi-ventricular disease, we compared these results with those of 29 symptomatic patients with isolated AR and with 18 symptomatic patients with isolated MR, all also undergoing valve replacement. Before operation, patients with AR/MR had significantly lower left ventricular (LV) ejection fraction than patients with MR (rest, $40 \pm 9\%$ vs $52 \pm 10\%$, $p < 0.025$; exercise, $35 \pm 12\%$ vs $54 \pm 12\%$, $p < 0.005$) and tended to have lower LV ejection fraction than patients with AR alone (rest, $40 \pm 9\%$ vs $45 \pm 12\%$, difference not significant; exercise, $35 \pm 12\%$ vs $39 \pm 11\%$, difference not significant); right ventricular (RV) ejection fraction was lower in AR/MR than in AR ($p < 0.01$), and tended to be lower than in MR (difference not significant). At average postoperative follow-up of 72 to 76 months (survivors in each group), symptomatic patients with AR/MR had significantly poorer survival than symptomatic patients with isolated MR ($p < 0.05$) and were more likely to have persistent symptoms than patients with AR ($p < 0.05$). These findings suggest that symptomatic patients with AR/MR have poorer LV and RV performance than similarly symptomatic operative candidates with AR or MR alone. These findings are paralleled by poorer operative outcome, in terms of survival and symptom persistence, in the AR/MR group.

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Long-term survival after operative relief of combined aortic and mitral regurgitation (AR/MR) has been relatively poor, and considerably worse than after valve replacement for isolated AR or MR alone.^{1,2} The basis for this discrepancy is unclear. One possible explanation is that, among comparably symptomatic patients presenting for valve replacement, ventricular dysfunction may be more marked and possibly less reversible among those with the double-valve lesion.³ This possibility is difficult to evaluate as left ventricular (LV) and right ventricular (RV) performance patterns among patients with AR/MR, without confounding stenoses, have not been systematically studied. Therefore, we have defined ventricular performance characteristics in a small but carefully studied cohort of symptomatic candidates for double-valve replacement with AR/MR, but without other valvular or coronary abnormalities, and have compared these findings with those of similarly symptomatic patients with isolated AR or MR alone. Finally, we have assessed the extent to which preoperative ventricular performance descriptors for each of the 3 subsets parallels relative postoperative outcome among the 3 groups.

METHODS

Patient population: The study population comprised 55 patients, first assessed between October 1979 and May 1985, with angiographic and clinical evidence of hemodynamically important chronic AR (29 patients), MR (18 patients) or AR/MR (8 patients) who manifested clinical evidence of at least New York Heart As-

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sociation functional class II "heart failure" symptoms without clinical history of myocardial infarction or angina pectoris, and who underwent valve replacement. These patients represent a consecutive series of those meeting study criteria who had been admitted to our ongoing prospective study of the natural course of regurgitant valvular disease. Symptoms were the indication for operation in all patients. Thus, although objective ventricular performance characteristics may have varied among these patients, they were relatively similar clinically. The population consisted of 36 men and 19 women ranging in age from 20 to 76 years (mean 53). Demographic characteristics, disease etiology and medication use before and after operation are listed in Table I. Of note, medication distribution was statistically indistinguishable among the 3 valve disease groups.

The diagnosis of hemodynamically important regurgitation was made at cardiac catheterization in all 55 patients on the basis of finding angiographic 3+/4+ or 4+/4+ AR and/or MR.⁴ Any patient with coexistent aortic or mitral stenosis was excluded. None of the 52 patients who underwent coronary arteriography had angiographic coronary artery disease, i.e., a $\geq 50\%$ decrease in luminal diameter in ≥ 1 major coronary artery. Patients failing to manifest functional class II symptoms were excluded from this analysis to maximize comparability of operative indications in the population; no uniform criteria for operation were apparent among asymptomatic patients and bias toward selection of symptomatic patients for operation could be expected, potentially skewing comparisons in which asymptomatic patients were included. The distribution of symptom severity among subgroups is shown in Figure 1. According to the study protocol, patients underwent M-mode and 2-dimensional echocardiography at rest, as well as radionuclide cineangiography at rest and during exercise. The mean interval between radionuclide study and echocardiography was 10 days (range 0 to 240). No important interval change occurred clinically between these tests. Informed consent was obtained from all patients per protocol approved by the Committee on Human Rights in Research of Cornell University Medical College. Twenty volunteers without clinical or electro-

TABLE I Population Characteristics

	AR	AR/MR	MR
No.	29	8	18
Male/female	23/6	6/2	8/10
Age (range/mean, yrs)	20 to 73/51	34 to 67/52	29 to 71/55
Etiology of valve disease			
Rheumatic	9	3	3
Mitral valve prolapse	0	0	12
Connective tissue disease	10	3	0
Congenital	4	0	0
Infective endocarditis	2	1	0
Autoimmune process	2	0	1
Ruptured chordae	0	0	2
Idiopathic	2	1	0
BSA (m ²)	1.86 $\pm$ 0.21	1.69 $\pm$ 0.19	1.75 $\pm$ 0.17
Heart rate (beats/min)	76 $\pm$ 10	79 $\pm$ 16	81 $\pm$ 11
Systolic BP (mm Hg)	156 $\pm$ 25 [†]	131 $\pm$ 12	128 $\pm$ 12
Diastolic BP (mm Hg)	68 $\pm$ 16*	65 $\pm$ 13*	82 $\pm$ 8
Pump time (min)	99 $\pm$ 27 [‡]	166 $\pm$ 39*	93 $\pm$ 15
X-clamp time (min)	73 $\pm$ 18 [‡]	108 $\pm$ 16*	64 $\pm$ 14
Medications	Pre/Postoperative		
Digoxin	19/16	7/6	11/12
Diuretics	13/10	3/3	7/11
Vasodilators	4/4	2/0	4/1
Calcium antagonists	1/1	0/0	1/1
β blockers	3/7	1/1	0/1
Antiarrhythmics	1/9	1/3	0/1

Data are mean $\pm$ standard deviation. Body surface area (BSA), heart rate and drug distributions did not vary significantly on intergroup comparison.

* $p < 0.01$ vs mitral regurgitation (MR); [†] $p < 0.05$ vs combined aortic and mitral regurgitation (AR/MR); [‡] $p < 0.01$ vs AR/MR.

BSA = body surface area; BP = blood pressure; X-clamp = cross-clamp.

cardiographic evidence of cardiopulmonary disease provided normal data (Table II) for both radionuclide cineangiography (20 volunteers) and echocardiography (18 of 20 volunteers); these values agreed well with those previously obtained by investigators in our group using similar methods in earlier normal series.^{5,6}

Echocardiographic studies: M-mode and 2-dimensional echocardiograms were performed in our laboratory in 52 of the 55 patients, using either ATL or Picker ultrasonoscope in the left lateral decubitus position with standard techniques.⁶ Simultaneous systolic blood pressure, measured by cuff sphygmomanometry, was recorded in all but 5 patients. Dimensions and wall thick-

FIGURE 1. Pre- (preop) and postoperative symptom status of 3 patient groups as per New York Heart Association (NYHA) classification. AR = aortic regurgitation; AR/MR = combined aortic and mitral regurgitation; COD = apparent cause of death; CVA = cerebrovascular accident; D = dead; FC = functional class; Met Ca = metastatic carcinoma; MR = mitral regurgitation; SBE = subacute bacterial endocarditis; SD = sudden death.

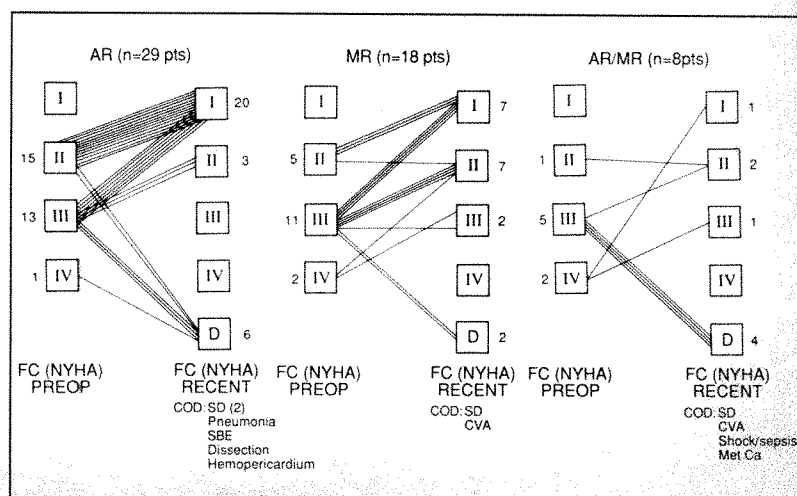


TABLE II Normal Data

Patient	LVIDI (cm/m ²)	LVIDSI (cm/m ²)	FS	ESS (dynes cm ² × 10 ³)	LVMI g/m ²	LVEFR (%)	LVEFX (%)	LVEFD (%)	RVEFR (%)	RVEFX (%)
1	2.5	1.5	38	49	65	53	77	24	50	NA
2	2.6	1.7	37	65	82	56	80	24	50	68
3	2.8	1.8	36	80	92	51	69	18	45	62
4	2.9	2.	32	93	85	55	66	11	46	62
5	3.	2.2	28	99	89	55	78	23	40	63
6	2.5	1.7	35	48	76	57	66	9	47	55
7	3.	2.1	29	135	97	50	64	14	46	58
8	2.5	1.6	35	82	77	46	62	16	42	65
9	2.7	1.7	38	69	49	51	59	8	36	50
10	2.7	1.8	33	88	73	51	67	16	50	55
11	2.7	1.8	35	58	37	46	59	13	44	55
12	2.5	1.7	34	68	42	46	65	19	44	65
13	2.9	2.	30	84	106	52	65	13	45	53
14	3.	1.8	40	84	108	47	56	9	38	56
15	3.1	1.9	38	84	113	52	69	17	NA	NA
16	2.6	2.	27	91	101	50	66	16	45	51
17	3.2	2.2	30	79	112	49	66	17	NA	NA
18	NA	NA	NA	NA	NA	50	65	15	48	61
19	NA	NA	NA	NA	NA	47	59	12	48	54
20	2.7	1.8	32	86	110	56	69	13	35	52
Mean	2.8	1.9	33	80	84	51	66	15	44	57
	0.2	0.2	4	20	24	4	6	5	5	6

ESS = end-systolic stress; FS = fractional shortening; LVEFD = difference between rest and exercise left ventricular ejection fraction; LVEFR = left ventricular ejection fraction at rest; LVEFX = left ventricular ejection fraction at maximal exercise; LVIDI = left ventricular diastolic dimension index; LVIDSI = left ventricular systolic dimension index; LVMI = left ventricular mass index; RVEFR = right ventricular ejection fraction at rest; RVEFX = right ventricular ejection fraction at maximal exercise.

nesses were measured at end-diastole and end-systole according to American Society of Echocardiography recommendations,^{7,8} LV mass was calculated by the anatomically validated Penn convention⁹ and end-systolic meridional wall stress was determined by the catheterization-validated method of Reichek et al.¹⁰

Radionuclide cineangiography: Radionuclide cineangiography was performed in all 55 patients according to a method analogous to our previously described electrocardiogram-gated equilibrium procedure,^{5,11} with patients in the supine position at rest and during exercise, as described in earlier reports of results from our regurgitant valve disease protocol.^{12,13} Supine bicycle ergometry was continued until limited by dyspnea, fatigue or chest pain. LV ejection fraction at rest and during

exercise was determined according to standard count-based methods, while RV ejection fraction at rest and during exercise was determined by the method of Madhahi et al.¹⁴ Both LV and RV ejection fraction determinations have been validated in our laboratory with reference to contrast videodensitometric determinations.^{15,16} LV ejection fraction determination was available in all 55 patients; RV ejection fraction was unavailable for analysis in 3 of the 29 patients with isolated AR, although it was available in all other patients.

Cardiac catheterization: All patients with MR or AR/MR and 28 of the 29 patients with AR underwent standard left-sided heart catheterization for hemodynamic and contrast ventriculographic study; 1 patient with AR underwent contrast angiography alone. How-

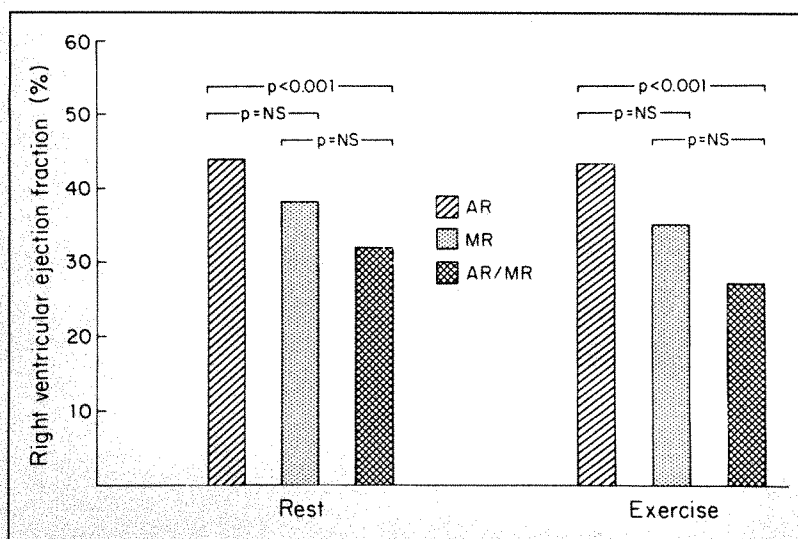


FIGURE 2. Preoperative right ventricular function at rest and during exercise among the 3 groups of patients. NS = not significant; other abbreviations as in Figure 1.

TABLE III Ventricular Function, Size and Load in Patients with Isolated or Combined Aortic and Mitral Regurgitation

	Group 1			Group 2			Group 3		
	AR		Group 1 vs 2 AR vs AR/MR	AR/MR		Group 2 vs 3 AR/MR vs MR	MR		Group 1 vs 3 AR vs MR
	n	(mean $\pm$ SD)		n	(mean $\pm$ SD)		n	(mean $\pm$ SD)	
LVEF %									
Rest	29	45 $\pm$ 12*	NS	8	40 $\pm$ 9*	p < 0.025	17	52 $\pm$ 10	NS (p < 0.10)
Exercise	29	39 $\pm$ 11*	NS	8	35 $\pm$ 12*	p < 0.005	18	54 $\pm$ 13*	p < 0.001
Δ LVEF	29	-6 $\pm$ 5*	NS	8	-5 $\pm$ 5*	p < 0.005	17	1.3 $\pm$ 5*	p < 0.01
RVEF %									
Rest	26	43 $\pm$ 8	p < 0.01	8	32 $\pm$ 8*	NS	18	38 $\pm$ 9*	NS
Exercise	26	43 $\pm$ 10*	p < 0.005	8	27 $\pm$ 16*	NS	18	35 $\pm$ 10*	NS
Δ RVEF	26	-0.8 $\pm$ 6*	NS	8	-5.6 $\pm$ 11*	NS	18	-3 $\pm$ 2*	NS
LVIDdi (cm/m ²)	28	3.8 $\pm$ 0.7†	NS	6	4.4 $\pm$ 1.1†	p < 0.001	18	3.6 $\pm$ 0.6†	NS
LVIDsi (cm/m ²)	28	2.9 $\pm$ 0.6†	NS	6	3.1 $\pm$ 0.9†	p < 0.001	18	2.2 $\pm$ 0.4†	p < 0.005
FS %	28	26 $\pm$ 6*	NS	6	28 $\pm$ 10*	p < 0.001	18	37 $\pm$ 7	p < 0.005
LVMi (g/m ²)	28	206 $\pm$ 65†	NS	6	189 $\pm$ 83†	NS	17	145 $\pm$ 44†	p < 0.005
ESS (dynes/cm ² $\times$ 10 ³)	28	140 $\pm$ 50†	NS	6	135 $\pm$ 63†	p < 0.001	17	80 $\pm$ 27	p < 0.001

* significantly less than normal population; † significantly more than normal population.

EF = change in ejection fraction from rest to exercise; ESS = end-systolic stress; FS = fractional shortening; LVEF = left ventricular ejection fraction; LVEFR = left ventricular ejection fraction at rest; LVIDdi = left ventricular internal dimension diastole; LVIDsi = left ventricular internal dimension index in systole; LVMi = left ventricular mass index; NS = not significant; Δ RVEF = change in right ventricular ejection fraction; SD = standard deviation.

ever, 1 patient with AR underwent catheterization 5 years before operation; her hemodynamic data were excluded from this analysis. Of the 27 AR patients with evaluable left-sided heart catheterization data, 25 also underwent right-sided heart catheterization; all patients with MR or AR/MR underwent right-sided heart catheterization. Cardiac output was determined by the Fick method in all but 1 patient in whom the measurement was performed; the single exception underwent thermolabeling assessment. Forty-nine patients also underwent supavalvular aortography, including all patients with AR and AR/MR and 12 of 18 patients with MR. Selective coronary arteriography was performed in 52 of the 55 patients; the 3 exceptions (2 AR, 1 AR/MR) were <35 years old. The mean intervals separating cardiac catheterization from evaluable radionuclide and echocardiographic studies were 49 days (range 0 to 345) and 47 days (range 0 to 345), respectively. There was no important interval change between noninvasive

studies and catheterization, except in 1 patient with AR who progressed from functional class II to functional class III during the 10 months before angiography.

Operation: No patient underwent valve replacement before the operation reported in this study. Operation was performed at The New York Hospital in 53 of the 55 patients. In these patients, either cold potassium cardioplegia or cold blood cardioplegia invariably was used for myocardial protection. In the 2 patients who underwent operation at other institutions, both with AR, myocardial preservation techniques are not known. All 8 patients with AR/MR underwent replacement of both valves (3 with Bjork-Shiley prostheses in both positions, 5 with Carpentier-Edwards bioprostheses in both positions). All 29 patients with isolated AR underwent single-valve replacement (18 with Carpentier-Edwards bioprostheses, 9 with Bjork-Shiley prostheses, 2 with St. Jude prostheses). However, 1 of these patients developed a marantic (noninfectious) vegetation on the mi-

FIGURE 3. Survival after operation among the 3 patient groups. Survival is indicated as a percentage on the ordinate. Abbreviations as in Figure 1.

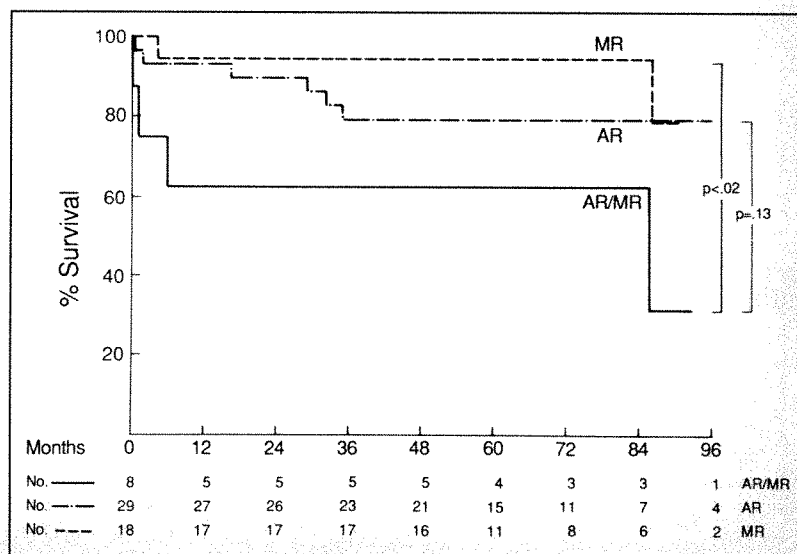


TABLE IV Hemodynamic Data

	Group 1		Group 1 vs 2	Group 2		Group 2 vs 3	Group 3		Group 3 vs 1
	n	AR	AR vs AR/MR	n	AR/MR	AR/MR vs MR	n	MR	MR vs AR
PAP (mm Hg)									
Systolic	25	36 ± 16	NS	8	50 ± 16	NS	18	41 ± 17	NS
Diastolic	25	16 ± 10	NS	8	22 ± 9	NS	18	20 ± 10	NS
Mean	25	24 ± 12	NS	8	32 ± 10	NS	18	30 ± 12	NS
PCWP (mm Hg)	26	15 ± 9	NS	8	18 ± 9	NS	18	20 ± 7.5	NS
LVEDP (mm Hg)	27	18 ± 10	NS	8	17 ± 8	NS	18	19 ± 10	NS
RVEDP (mm Hg)	23	11 ± 12	NS	8	10 ± 6	NS	17	8 ± 6	NS
CI (liters/min/m ²)	25	2.8 ± 0.7	NS	8	2.3 ± 0.5	NS	16	2.5 ± 0.8	NS

CI = cardiac index; LVEDP = left ventricular end-diastolic pressure; NS = not significant; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RVEDP = right ventricular end diastolic pressure. Other abbreviations as in Table I.

tral valve subsequent to aortic valve replacement, required mitral valve replacement and died 1 month after the second operation. For purposes of analysis, this patient is considered to be in the single-valve replacement AR group. All 18 patients with isolated MR underwent single-valve replacement (Carpentier-Edwards porcine bioprostheses in 9, Bjork-Shiley prostheses in 8 and Starr-Edwards prosthesis in 1). One patient with AR/MR underwent concomitant tricuspid annuloplasty and no patient had tricuspid valve replacement.

Follow-up: Per protocol, patients were followed with annual visits to study physicians for an interview and physical examination. If annual visits were not kept, or if additional intervisit information was deemed useful, telephone calls and communication with referring physicians were used. Follow-up information is available for all patients (duration noted later).

Statistical methods: Data are expressed as the mean ± standard deviation. Significance of differences between group means was assessed by 1-way analysis of variance. Intergroup differences thus identified subsequently were analyzed using the Tukey test for multiple

comparisons. Strength of correlations was assessed by the least squares linear correlation method. Significance of differences in frequency of events among groups was assessed by Fisher's exact test. Death rates were compared by life-table analysis and analyzed according to the generalized Wilcoxon (Breslow) statistics.¹⁷⁻¹⁹

RESULTS

Left ventricular performance and dimensions: At rest, mean LV ejection fraction in patients with isolated MR was statistically indistinguishable from normal and was significantly higher than among patients with AR/MR; in the latter group, moreover, mean LV ejection fraction was subnormal (Table III). Patients with AR/MR tended toward lower LV ejection fraction than with AR alone, although the latter difference did not achieve statistical significance. Similarly, the prevalence of subnormal resting LV ejection fraction tended to be greater among patients with AR/MR (63%) than among patients with MR alone (24%, $p = 0.087$) or with AR alone (48%, difference not significant). At peak exercise in all 3 patient groups, LV ejection fraction was subnormal, with significantly lower values in the AR/MR and AR groups than in patients with isolated MR. LV functional reserve, as estimated by change in ejection fraction from rest to exercise, was subnormal for all 3 groups, though patients with AR/MR or with AR alone manifested significantly greater subnormality than patients with MR alone. The group patterns in radionuclide-based performance characteristics were paralleled in results of echocardiography, which revealed depressed fractional shortening among patients with AR and AR/MR, but a trend toward supernormal fractional shortening among patients with isolated MR. Depressed resting LV performance in AR and AR/MR patients could be at least partially attributed to elevated myocardial afterload as evidenced by substantially supernormal end-systolic stresses, while this measure of ventricular afterload was normal in patients with isolated MR. However, the tendency toward worse LV performance in AR/MR than in AR could not be explained on the basis of afterload differences, as end-systolic stress was virtually identical in these 2 subgroups. Consistent with this observation, the ejection fraction/end-systolic stress relation for all evaluable patients suggests a relative deficiency in LV performance among AR/MR patients over any given stress range.

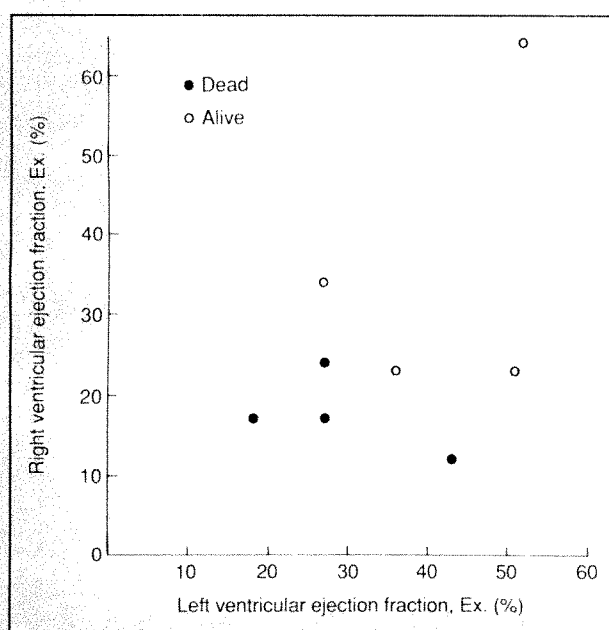


FIGURE 4. Relation of outcome in combined aortic and mitral regurgitation to preoperative left and right ventricular performance during exercise. EX = exercise.

Indexed LV internal dimensions at end-diastole were supernormal in all groups, although patients with combined AR/MR had more marked LV dilatation than patients with MR alone ($p < 0.001$) or AR alone ($p < 0.1$). Similarly, indexed dimensions at end-systole among AR/MR patients were significantly greater than in patients with isolated MR. LV mass index was supernormal in all groups. Moreover, mass index in MR was significantly less than in the AR group ($p < 0.005$).

Right ventricular performance: On average, RV ejection fraction at rest was normal in the AR group, but was significantly subnormal among patients with MR alone or with AR/MR. Both at rest and during exercise, RV ejection fraction in the AR/MR group was significantly lower than in patients with isolated AR and tended to be lower than in MR alone (Figure 2). The prevalence of subnormal RV ejection fraction among patients with AR/MR (63%) was significantly ($p < 0.001$) higher than among patients with AR alone (8%) and tended to be higher than that among patients with MR alone (28%, difference not significant). Symptom status did not appear to predict differences in RV performance among our patient groups. Thus, among patients with preoperative functional class III, RV performance at rest and during exercise was significantly worse among the AR/MR group than that among patients with isolated AR ($p < 0.05$ at rest; $p < 0.01$ during exercise) and tended to be worse than in patients with isolated MR; LV performance both at rest and during exercise was significantly worse in AR/MR patients than those with isolated MR ($p < 0.011$ at rest, $p < 0.0012$ during exercise) and was more depressed, but not significantly so, than in patients with isolated AR.

Hemodynamics: Among patients with AR/MR, pulmonary pressures were similar to those among patients with isolated MR; for both groups, pulmonary pressures generally were higher than those among patients with isolated AR (Table IV). Patients with AR/MR tended to manifest the lowest cardiac index among the 3 groups.

Postoperative survival: Among the 8 patients with AR/MR (postoperative follow-up 52 to 103 months for survivors, average 76), 4 (50%) are dead. In contrast, of the 29 patients with AR, 6 patients (21%) are dead (postoperative follow-up 42 to 115 months for survivors, average 73); of the 18 patients with MR, 2 (11%) have died (postoperative follow-up 40 to 101 months for survivors, average 72). Clearly, the relatively small number of deaths in each group precludes confidence in absolute survival rates definable from these data. Nonetheless, life-table analysis of group patterns regarding relative frequency of events (Figure 3) indicates that symptomatic patients with AR/MR have significantly poorer survival after operation than do symptomatic patients with MR and tend to have poorer survival than symptomatic patients with AR.

Postoperative symptom status: As previously noted, before operation, all patients manifested symptoms of New York Heart Association functional class II or worse. At the most recent postoperative follow-up (Figure 1) 3 of 4 surviving patients with AR/MR continued in class II or worse; 7 of the 8 patients who underwent

operation either were symptomatic or dead. Of 16 survivors with MR, 9 were persistently symptomatic and 11 of 18 symptomatic or dead; while these data suggest less unfavorable postoperative outcome in MR than in AR/MR, endpoint proportions were not significantly different. In contrast, of 23 survivors with AR, only 3 were symptomatic ($p < 0.03$ vs AR/MR); 9 of 29 were either symptomatic or dead ($p < 0.02$ vs patients with AR/MR).

We were unable to define statistically significant predictors of mortality or of postoperative symptom status in the small group of patients with AR/MR, although as a group, the 4 patients who died after operation tended to manifest lower RV and LV ejection fractions during exercise than did survivors and all 3 with RV ejection fraction $< 20\%$ during exercise died (Figure 4).

DISCUSSION

Our data indicate that when patients with hemodynamically severe combined AR/MR develop symptoms of at least moderate severity, both RV and LV performances generally are subnormal and, considered together, are significantly worse than in similarly symptomatic operative candidates with AR or MR alone.

Although these findings intuitively may seem predictable, the hemodynamics of combined regurgitation are complex. As suggested by Kirklin et al,³ the low impedance outflow pathway from the LV due to MR might be expected to mitigate the effects of AR/MR-induced volume loading. However, few data are available to document LV performance from previous studies of patients with AR/MR uncontaminated by confounding stenoses. Thus, our findings uniquely document that pure AR/MR, at least in the symptomatic operative candidate, frequently is associated with subnormal LV performance. Moreover, our finding of particularly depressed RV performance, not previously assessed in AR/MR, parallels our earlier findings in isolated MR.¹²

Given our relatively small AR/MR population, any inferences regarding the relation between objective findings and outcome must be considered preliminary. Nonetheless, the mortality rate in our small series was comparable to that previously reported in the earlier investigation involving a specifically defined pure AR/MR subset.³ Similarly, the rank order of postoperative survival rates among our 3 patient subgroups is consistent with previous reports.^{3,20-22} Moreover, consistent with our survival data, persistence of symptoms after operation also was more frequent among patients with combined rather than those with isolated regurgitant lesions. Given the parallelism between results of preoperative ventricular performance and postoperative outcome, our data suggest the importance of ventricular performance assessment in optimizing the timing of valve replacement for AR/MR. This conclusion is consistent with the several studies that have related preoperative LV performance to postoperative survival in patients with isolated MR²³ and AR,²⁴⁻²⁷ and with our findings that RV ejection fraction is a particularly significant predictor of outcome in unoperated patients

with MR,¹² as well as a predictor of symptom status after mitral valve replacement.¹³

The relatively poor survival among AR/MR patients after operation may reflect factors other than preoperative ventricular function, including associated coronary artery disease, nonstandard myocardial protection methods and tricuspid valve replacement.³ Though our patients with AR/MR uniformly were free of these problems, myocardial damage systematically attendant to double-valve replacement might account in part for the outcome we observed.

Our data raise important questions regarding the use of clinical descriptors alone in selection of AR/MR patients for operation. Although our small numbers mandate a cautious interpretation, our results suggest that when conventional symptom-based criteria for valve replacement are met among patients with AR/MR, RV and LV dysfunction generally is more severe than among similarly symptomatic patients with single-valve regurgitation. This observation may account at least in part for the relatively poor postoperative results commonly reported and suggests the need to reevaluate risk/benefit considerations regarding operation earlier in the natural history of AR/MR than now is the norm.

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The "Laid-Back" Aortogram: An Improved Angiographic View for Demonstration of Coronary Arteries in Transposition of the Great Arteries

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Preoperative demonstration of coronary arterial anatomy may be important for babies undergoing the arterial switch operation. Echocardiography is clearly useful, but may not unequivocally show all coronary branches. Standard angiographic views can be confusing. An improved angiographic projection in which the frontal x-ray tube is caudally angled, resulting in a "laid-back" position of the image intensifier and cine camera, provides superior visualization of the coronary arteries and their relation to the aorta and the pulmonary artery. The balloon occlusion technique is used for opacification of the aortic root from the transvenous approach. Injection of 1 ml/kg of contrast delivered in 1/2 to 1 second provides the best images. The caudal aortogram is easier to interpret than standard views and facilitates description and recognition of various coronary patterns. The relation between the pulmonary artery and the aorta, the origins of the coronary arteries from the facing sinuses and their proximity to the intercoronary commissures, and the myocardial distribution of each coronary vessel are shown clearly. The caudal view therefore offers significant advantages over conventional projections for demonstration of coronary arterial anatomy in infants with transposition of the great arteries or double-outlet right ventricle.

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An accurate preoperative definition of coronary artery anatomy may be important in infants with transposition of the great arteries or double-outlet right ventricle who are being evaluated for the arterial switch operation. Echocardiography¹ and aortic root angiography² in standard projections have been used to define the coronary arterial anatomy. However, echocardiography sometimes fails to show all coronary vessels and interpretation of conventional aortograms sometimes can be difficult. We recently developed an improved angiographic technique using balloon aortography combined with extreme caudal angulation to outline the coronary arterial anatomy in transposition of the great arteries. A caudally angled left anterior oblique aortogram was described in 1975 by Stein and Sabbah,³ who coined the term "orifice view" for improved visualization of the aortic valve. We have used the caudally angled balloon occlusion aortogram in arterial switch candidates to improve visualization of the coronary arterial origins and distribution and have found that this view facilitates their description as well.

METHODS

A consecutive series of 19 patients with transposition of the great arteries and 1 patient with double-outlet right ventricle who underwent preoperative echocardiography and cardiac catheterization are the basis for this study. Their ages ranged from 1 day to 18 months. Thirteen patients were <1 year of age and 7 were <1 month old. The average weight was 3.8 kg (range 2.8 to 8.5).

All patients had aortography as part of their diagnostic catheterization. A 5Fr Berman catheter, introduced transvenously, was positioned in the ascending aorta using frontal and lateral fluoroscopy. The frontal x-ray tube and image intensifier were then "laid-back," that is, caudally angled, generally 40 to 45° (Figure 1, upper panel). In some cases, a slight left or right anterior oblique orientation was used to further foreshorten the ascending aorta. The lateral tube and image intensifier were not moved.

Using the lateral tube for fluoroscopy, the balloon catheter was positioned in the ascending aorta proximal to the innominate artery so that the sideholes were approximately 0.5 to 1.0 cm above the aortic valve. This technique has been described in detail previously.² The catheter was then connected to the injector and flushed

with contrast. The balloon was inflated with carbon dioxide until it became somewhat stationary, indicating that it fit the lumen of the ascending aorta (Figure 1, lower left). A power injection was made for cine filming using both cameras. The balloon was then deflated immediately after the injection, but while the cine camera was still running. A drawing of the view as "seen by" the frontal, caudally angled camera is shown in Figure 1 on the lower right.

Contrast agents used for aortography in this series of patients included ioxaglate sodium-meglumine (Hexabrix, Mallinckrodt), diatrizoate sodium-meglumine (Renovist, E.R. Squibb) and iohexol (Omnipaque, Winthrop-Breon Laboratories). Volumes and rates as prescribed by individual cardiologists ranged from 0.7 ml/kg injected in 1 second to 1.4 ml/kg injected in 0.4 second.

The primary purpose of this series was to evaluate the technical aspects of this method of aortography. Thus, angiograms were reviewed retrospectively by the investigators for diagnostic quality and clarity of coro-

nary display. Injection rates and volumes were evaluated to ascertain the most effective technique. In addition, the precatheterization echocardiogram reports and operative notes were reviewed to correlate their findings with those at angiography.

RESULTS

Angiographic technique: In reviewing the first 20 angiograms, we found that 11 patients required a second aortogram to improve technique. As we became more familiar with the catheter and balloon position, as well as the rate and volume for optimal images, we were able to obtain excellent images with only 1 injection in most subsequent cases. In this series, the 2 oldest patients, ages 15 and 18 months, had the least satisfactory angiograms largely due to difficulty in completely occluding the ascending aorta. It also became apparent that, in general, the frontal camera should be caudally angled with, at most, minimal right or left anterior oblique orientation. The latter can cause the aortic arch to overlap the left side of the aortic root and interfere

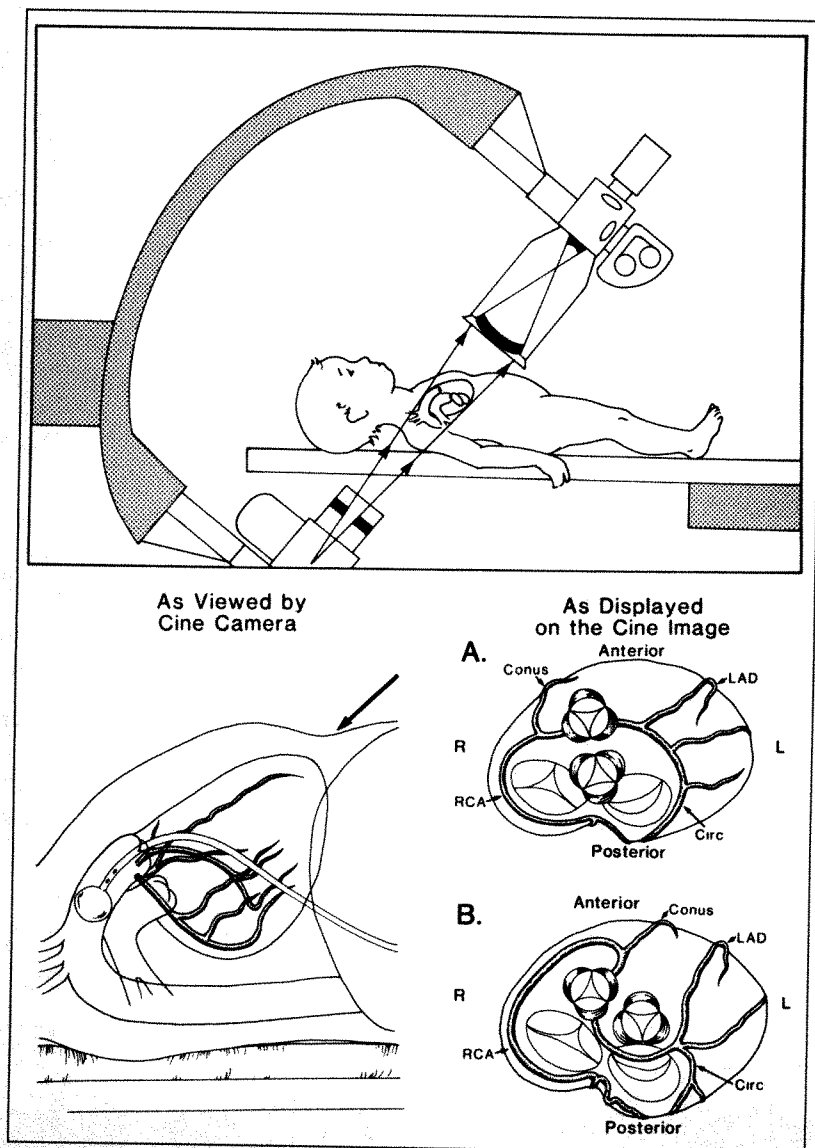


FIGURE 1. Upper panel, position of frontal C-arm with extreme caudal angulation of the tube. The lateral tube, necessary for balloon positioning, is not shown. Lower left panel, view of heart and balloon position as "seen" by lateral image intensifier. Solid arrow in right upper corner shows "viewpoint" of frontal camera when it assumes its caudal angulation. Lower right panel, caudal view of heart and coronary arteries as displayed by frontal cine camera. An example of coronary course in front-to-back (A) and side-to-side (B) great arteries is shown. Circ = circumflex artery; LAD = left anterior descending artery; RCA = right coronary artery.

with optimal visualization of the coronary origins from the sinuses.

In reviewing the volume and rate of contrast used in each patient and comparing it to the quality of the angiogram, we concluded that a volume of 1 ml/kg delivered in $\frac{1}{2}$ to 1 second provided the best images. Slower injection rates did not adequately opacify the coronary arteries, while larger volumes at higher rates produced some aortic regurgitation. The quality of the image was significantly diminished if there was spill of contrast into the ventricle. The image was also less satisfactory if excessive contrast was delivered into the arch vessels at the beginning of the injection. This usually was due to either insufficient obstruction of the ascending aorta, or placement of the balloon too far distally. In general, the images were best in the infants in whom the ascending aorta was smallest and therefore easiest to occlude. In 2 patients, contrast injection was made using a retrograde pigtail catheter; although images were still diagnostic, they were not as clear due to overlapping arch vessels.

We subjectively graded the aortograms for degree of coronary opacification and clarity of coronary display. Fifteen were considered good to excellent, 4 were satisfactory and 1 was poor because the catheter recoiled into the right ventricle.

Interpretation: We found that interpretation of the caudal view was facilitated because there was no overlap of coronary branches (Figures 2, 3 and 4). Even in those aortograms judged to be only satisfactory in quality, the origin and course of all major coronary branches—left anterior descending, circumflex and right coronary artery—were clearly and easily discernible. The origin of the coronary artery with respect to the commissure could be seen, particularly with the motion of cine (Figure 3A). The distribution of each coronary artery, i.e., the relative amount of myocardium supplied by each, was clearly shown.

The initial case in this series, depicted as number 10 in Figure 5, had an intramural coronary artery suspected at echocardiography. The caudal aortogram was conceived to clarify this anatomy angiographically. The images from that first case did not lend themselves to a single-frame reproduction. However, more recently, another case of intramural coronary artery was shown by this method and the angiogram of that patient, who also had essentially a single coronary orifice, is shown in Figure 4.

Anatomy and descriptive terminology: Figure 5 shows the coronary arterial patterns of our first 20 patients. It became apparent that the easiest way to describe the coronary anatomy was to state first whether the great arteries were in a relatively front-to-back relation (cases 11 to 20, Figure 5) or in a relatively side-to-side relation (cases 1 to 10, Figure 5). In the former, the coronary arteries could be described as originating from the left posterior-facing sinus or right posterior-facing sinus. In the latter (side-to-side), the coronary arteries could be described as originating from the anterior-facing sinus or posterior-facing sinus. Of patients with more of a front-to-back relation, 9 of 10 had the "usual" coronary anatomy for transposition, as shown in

Figure 5. We found, as have others, that patients in whom the great arteries were in a more side-to-side relation had considerable variation in coronary anatomy.⁴ A recent review of our arterial switch patients suggests that when the major coronary supply to the left ventricle courses around posterior to the pulmonary artery, there has been thus far an increased risk for early and late mortality.⁵

Correlation with echocardiograms and surgical findings: In all 20 patients, echocardiograms (Hewlett-Packard, Acuson) were performed and interpreted before angiography. We found that aortography using caudal angulation afforded superior detail in the evaluation of the coronary anatomy, especially the distal myocardial distribution. We consider the echocardiogram and aortogram complementary, since the echocardiogram, as it did in our first case, may predict an unusual coronary course, which then may be confirmed or further clarified at angiography.

We also reviewed the operative reports of all patients who underwent surgery. In no case did the surgical inspection reveal anatomy that was not predicted from the angiogram. Seventeen of the 20 patients underwent the arterial switch procedure. Two received pulmonary artery bands as temporary palliative procedures. One of these patients had multiple ventricular septal defects, and the other was the 1 patient in this series with double-outlet right ventricle (Figure 5, patient 4) with a rather uncommitted ventricular septal defect and mild pulmonary stenosis. The initial patient in the series who had the intramural coronary artery had an intact ventricular septum. Because of his unfavorable coronary anatomy, surgery has been deferred as of this study. The patient with the single intramural coronary artery, studied subsequent to these first 20 patients, was felt to have coronary anatomy unsuitable for the arterial switch operation and underwent a Senning procedure.

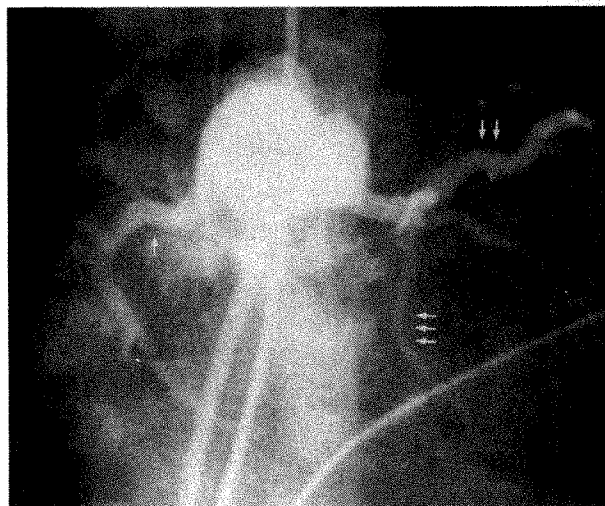


FIGURE 2. Laid-back view in patient with most common anatomy found in transposition of great arteries. Great arteries are front-to-back and the right coronary artery (single arrow) arises from right posterior-facing sinus and gives off a conal branch, while the left coronary artery arises from left-posterior-facing sinus and gives rise to left anterior-descending (double arrow) and circumflex arteries (triple arrow).

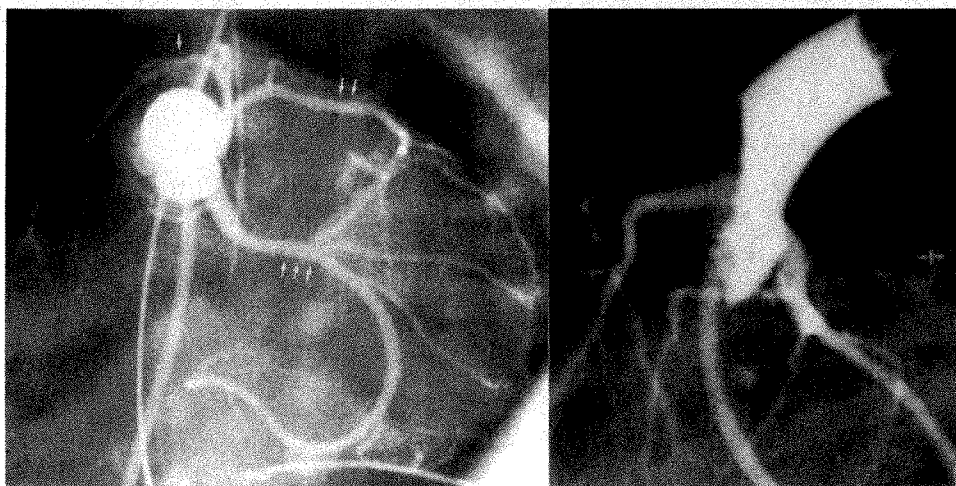


FIGURE 3. *Left*, caudal view in a patient whose great arteries are more side-by-side in relation and whose coronary anatomy is atypical. From anterior-facing sinus, a coronary artery originates and gives rise to the left anterior descending artery (*double arrow*), which crosses anterior to the pulmonary artery, and a small right coronary artery (*single arrow*), the latter essentially supplying only the conus. From the posterior-facing sinus arises a very dominant circumflex artery (*triple arrow*), which courses behind the pulmonary artery and supplies the lateral, posterior and inferior walls of the left ventricle. This view clearly shows the large amount of myocardium supplied by this vessel, far in excess of that supplied by the left anterior descending artery, which arises separately from the anterior-facing sinus. *Right*, lateral view of the same showing ideal balloon position and occlusion of the aorta at time of injection.

DISCUSSION

Anatomic considerations: Extreme caudal angulation is the essence of this angiographic view. The x-ray beam comes from the head of the table and aims caudally, toward the feet. This places the image intensifier in a position as if it were "looking" from the foot of the patient (Figure 1). The images obtained are very reminiscent of drawings presented in anatomy books in which the atrioventricular valves and semilunar valves

are displayed together (Figure 1, lower right panel). Using this view, one can see the front-to-back or side-to-side relation of the great arteries, the aortic sinuses and the origin of the coronary arteries relative to the commissures.

One particularly difficult coronary course to show angiographically has been that in which the coronary artery is partially intramural and courses between the 2 great arteries.⁶ The echocardiogram suggested this anatomy in our first case and this appearance was confirmed using the caudal view. The aortogram from 1 additional case (Figure 4) shows a single coronary artery arising from the right posterior-facing sinus giving rise to the right coronary artery, the circumflex artery, which goes behind the pulmonary artery, and the left anterior descending artery, which courses between the great vessels in a suspected intramural location. We doubt that this relation could have been depicted as graphically using standard aortography.

The caudally angled aortogram also allows superior demonstration of the proportional distribution of each coronary artery to the left ventricular myocardium because the right and left ventricles do not overlap in this view. Figure 3, for example, shows a patient in whom the circumflex artery, arising from the posterior-facing sinus, is extremely dominant, supplying the entire inferior, posterior and a good deal of the high lateral wall, while the left anterior descending artery, arising separately from the anterior-facing sinus, supplies only the anterior wall and apex. This degree of detail is not available from echocardiographic examination. Additionally, smaller, early branches (such as conal or sinoatrial nodal branch), which might hinder complete mobilization of the proximal vessel, are well displayed.

The caudal aortogram has certain limitations. Successful occlusion of the ascending aorta may be difficult

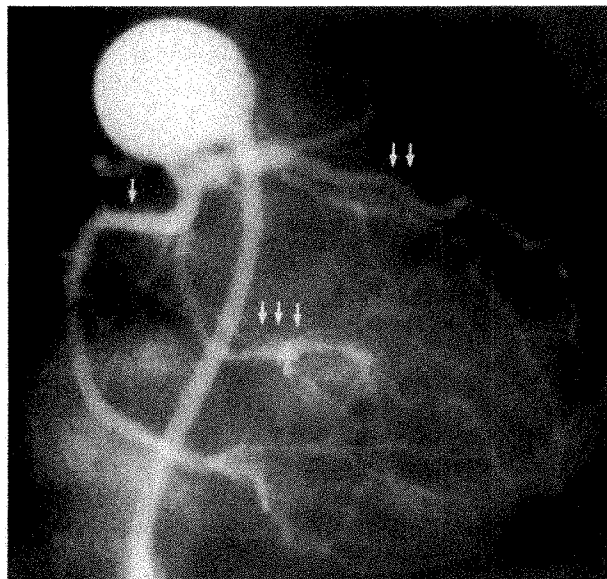
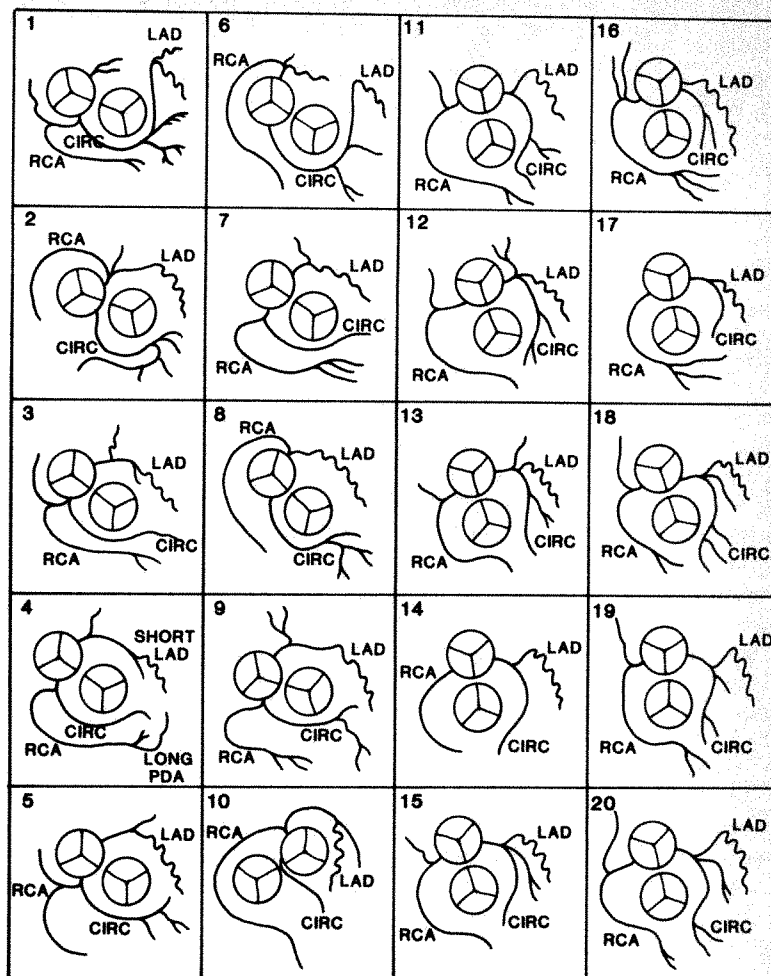


FIGURE 4. An aortogram from an infant with a front-to-back great artery relation. There is a single coronary orifice arising from the right posterior-facing sinus; this divides into the right coronary artery (*single arrow*), the circumflex artery (*triple arrow*), which goes behind the pulmonary artery, and the left anterior descending artery (*double arrow*), which goes between the aorta and the pulmonary artery in a suspected intramural course.

FIGURE 5. Coronary arterial patterns in the 20 cases. Drawings were made as seen by the caudal view, i.e., as viewed from below as shown in Figure 1. Drawings of cases 1 to 10 show infants in whom the great arteries were more side-to-side and drawings of cases 11 to 20 represent anatomy in infants with the more usual front-to-back relation. Note the posterior course of the circumflex artery in cases 1 to 10. LAD = left anterior descending artery; CIRC = circumflex artery; RCA = right coronary artery; PDA = posterior descending artery.



in patients outside the first few months of life and contrast injection must be such that the coronary arteries are outlined without producing aortic regurgitation. Moreover, the steep angulation necessary for the caudal view may become more difficult to achieve in a large patient. Nonetheless, this view provides superior angiographic visualization of the coronary origins and distribution and simplifies descriptive terminology of coronary anatomical patterns. As an adjunct to the echocardiographic examination, we now use the caudal aortogram to further define the coronary anatomy in patients who are candidates for the arterial switch operation.

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Usefulness of a Systemic Hypertension In-Hospital Educational Program

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The effects of an educational program on compliance and blood pressure (BP) control were assessed in 47 hypertensive patients hospitalized for nonhypertension-related diseases. Patients were randomized to receive either a questionnaire and an educational program (group I, 25) or questionnaire only (group II, 22). Baseline clinical characteristics, admission diagnoses and antihypertensive medications were similar between the groups. Antihypertensive medications used by patients before the trial were not changed. Eight weeks after the initial intervention, patients in group I showed a significant reduction in both systolic and diastolic BP (137/89 vs 154/98 mm Hg, $p = 0.005$ and 0.006 , respectively) and improved compliance (96 vs 36%, $p = 0.04$), compared with patients in group II. An education program in patients with high BP is an effective method to improve compliance and BP control in the short-term.

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Among the many causes for inadequate blood pressure (BP) control in hypertensive patients, poor compliance with the long-term pharmacologic treatment is the leading one.¹⁻³ Although new techniques have been developed to improve patient adherence to the therapeutic regimens,⁴ it continues an important clinical problem.⁵

Despite awareness about the reduction in hypertension-induced complications with the use of antihypertensive drugs,⁶ the complexity of the therapeutic regimens, high costs, side effects and poor patient-physician relations contribute to the finding that about 60% of low-income hypertensive patients do not comply with their therapy.⁷ Even provision of medical care at the work site proved to be noneffective in improving compliance.⁸

Simplification of the therapeutic regimen to a once-a-day dosing⁹ and educational interventions are better alternatives in improving compliance in hypertensive patients.¹⁰ Several educational programs to improve BP control through compliance in outpatient settings proved to be effective.¹¹⁻¹⁶ We report a randomized clinical trial designed to evaluate the short-term efficacy of an in-hospital educational program.

METHODS

Patient group: This study was performed in hospitalized patients with a known diagnosis of systemic hypertension. Patients were admitted to the Department of Internal Medicine at the San Juan City Hospital. Patients (26 women, 21 men) were aged 50 to 70 years (60 ± 10). Each patient gave informed consent to participate in the study.

Study design: During March and April 1989 there were 60 patients who met the inclusion criteria: adult, alert, literate, with known history of high BP, receiving antihypertensive therapy before and continued on admission, and with primary admission diagnoses not related to high BP. One patient refused to participate.

During the first 3 days after admission, a registered nurse measured BP 3 times a day for every patient. Both arms were positioned at the heart level, and BP was measured beginning ≥ 10 minutes after a quiet rest, in the sitting position. Appropriate cuff size and mercury sphygmomanometers were used. The level of appearance of S_1 was considered the systolic reading and the disappearance of the sounds (Korotkoff phase V) was considered the diastolic reading.¹⁷ From these readings, mean systolic and diastolic BP were calculated as baseline in every patient. After the third day, a questionnaire was presented by the health educator to each pa-

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tient to determine education and BP knowledge. After 4 days, the patients were randomized to receive the educational program (group I, 30) or not (control, group II, 29). We gave 4 educational interventions, 15 to 20 minutes each, in 2 days. The activities were: (1) "knowing high BP," offered by a physician, (2) "diet and high BP," offered by a registered dietitian, (3) "exercise and high BP," offered by a health educator and (4) "medications and compliance in high BP," offered by a physician and a pharmacy student. All activities took place in the conference room of the Department of Internal Medicine, in a classroom setting. All patients involved in the study continued receiving the antihypertensive drugs they were using before the trial, as ordered by their primary physicians, who were instructed not to alter the medications during the trial unless absolutely necessary.

Eight weeks after the interventions the patients were seen for the final evaluation. Again, 3 BP measurements were taken on each arm in every patient after a resting period ≥ 10 minutes. Mean systolic and diastolic BP were calculated for every patient and compared with baseline. The patients were then asked about compliance and side effects. Pill counts were used to confirm this information. During the 8-week-period that followed the first intervention 2 patients died, 1 in each group. Ten patients were lost to follow-up, 4 in group I and 6 in group II. The results evaluated the data of the remaining 47 patients (25 in group I, 22 in group II).

Statistical analysis: The results were analyzed using the Student unpaired *t* test for continuous variables, and chi-square and Fisher's exact test for differences between proportions, as appropriate. Data and results are expressed as mean $\pm$ standard deviation unless otherwise stated. A *p* value < 0.05 using the Mantel-Haenszel method for corrected *p* value was considered statistically significant. The variances are homogenous with 95% confidence limits.

RESULTS

The clinical features of the 25 patients in the educational program (group I) were compared with those of the 22 control patients (group II). There were no differences among the 2 groups in age, sex, duration of high BP, overweight patients, concomitant diseases and compliance (Table I). In group I, 92% of patients completed primary school, in group II, 90%; the remaining completed high school (difference not significant). None of the patients were college graduates.

No significant differences were found in primary admission diagnoses in both groups (Table II). There were no significant differences between the groups in the type of antihypertensive drugs they were using (Table III). Multidrug regimens were also similar. The 3 types of antihypertensive drugs most frequently used were diuretics (46%), calcium antagonists (31%) and angiotensin-converting enzyme inhibitors (25%). At baseline, 10 patients, 6 in group I and 4 in group II, did not know the antihypertensive drugs they were using (*p* = 0.63). At the end of the study, all patients knew their therapy (*p* = 0.008 vs baseline).

TABLE I Baseline Clinical Features of Patients

Variable	Group I	Group II	p Value
No. of pts	25	22	NS
Age (yrs)	60 $\pm$ 10	58 $\pm$ 12	NS
Sex (M/F)	11/14	10/12	NS
Duration of high BP (yrs)			
≤ 5	7	7	NS
≥ 6	18	15	NS
Overweight ($> 15\%$ IBW)	17	12	NS
Diabetes mellitus	8	6	NS
Coronary artery disease	3	4	NS
Malignancy	2	3	NS
Compliant (%)	30	20	NS

BP = blood pressure; IBW = ideal body weight; NS = not significant.

TABLE II Primary Admission Diagnoses of Patients

Diagnosis	Group I	Group II	p Value
Pneumonia	12	10	NS
Diabetes mellitus	7	5	NS
Pancreatitis	1	0	NS
Chemotherapy, cancer	2	3	NS
Urinary tract infection	2	2	NS
Systemic lupus erythematosus	0	1	NS
Cellulitis	1	1	NS

NS = not significant.

TABLE III Antihypertensive Drugs Used

Type of Drug	Group I	Group II	p Value
Diuretics	10	12	NS
Central adrenergic inhibitors	3	4	NS
α blockers	4	3	NS
β blockers	5	3	NS
Calcium antagonists	9	6	NS
Angiotensin-converting enzyme inhibitors	6	6	NS
Direct vasodilators	0	0	NS
Multidrug therapies	15	13	NS
Unknown by patients at baseline	6	4	NS

NS = not significant.

Before the interventions no significant differences were found in systolic (*p* = 0.30) and diastolic (*p* = 0.75) BP between the 2 groups. Eight weeks after the interventions, systolic and diastolic BP were significantly reduced among patients in group I (*p* = 0.005), but not in group II (*p* = 0.63) (Table IV). When asked about their adherence to the antihypertensive therapy, 24 patients in group I (96%) and 8 patients in group II (36%) gave positive responses (*p* = 0.04). This information was confirmed by pill count. Compared with baseline data, significant improvement in compliance was found in group I only (from 30 to 96%, *p* < 0.001).

DISCUSSION

The results of this study indicate that one of the most important factors to improve compliance with an-

TABLE IV BP in Both Groups at Baseline and Eight Weeks After the Educational Program

Blood Pressure Data (mm Hg)	Group I	Group II	p Value
Baseline			
Systolic BP	151 ± 23	144 ± 13	0.30
Diastolic BP	100 ± 13	101 ± 11	0.75
Follow-up (8 weeks)			
Systolic BP	137 ± 16	154 ± 30	0.005
Diastolic BP	89 ± 10	98 ± 11	0.006
Change from mean BP			
Systolic BP	-14	+10	0.001
Diastolic BP	-11	-3	0.010

BP = blood pressure.

tihypertensive drugs is patient education. An in-hospital educational program proved to be effective in improving compliance and controlling BP in known hypertensive patients receiving long-term antihypertensive regimens. Although previous studies evaluated compliance by counting pills, observing patient adherence to appointments and refilling medications at pharmacies,^{12,18} it has been reported that better ways to evaluate patient compliance are direct questioning and BP control.⁴ Both data were significantly different in the 2 groups, showing adequate control of BP and 96% compliance in patients receiving the educational program versus poor BP control and 36% compliance in the control patients ($p = 0.04$).

Schoenberger et al¹⁹ found that only half of the hypertensive patients aware of their condition were receiving adequate management. At baseline, we found that 20% of patients in group I and 18% in group II did not know the medications and doses they were receiving. These data suggest poor management secondary to lack of motivation among these patients. Similar to previous studies,^{1,2} we found other causes for noncompliance as pointed out by the patients in their questionnaire: high cost of medical and pharmaceutical care, lack of continuity of medical care, lack of adequate facilities, prolonged waiting times and adverse reactions to antihypertensive drugs. The more significant cause was the absence of patient motivation due to lack of an educational program. Schulman²⁰ and Nelson et al²¹ have reported "poor compliance" as a result of patient misconception about the importance of antihypertensive therapy. It has been specifically important in the elderly.⁹

As listed in Table IV, systolic blood pressure increased in the control patients by the end of the study. This incremental change has been previously reported by Zisner et al¹² in a private practice patient population. In this study it was most probably secondary to the loss, after discharge, of the regular schedule of antihypertensive drugs and the low-salt diet given to the patients while hospitalized.

We assessed the effects of an educational program at short-term (8 weeks). Although long-term programs could require more complex and expensive organiza-

tions, some investigators suggest that effective improvement in patient adherence to therapy may only need better use of resources.¹⁰ Even nonphysician health personnel¹³⁻¹⁸ providing a single intervention²² have been effective in improving compliance with antihypertensive regimens.

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Doppler Echocardiographic Flow Velocity Measurements in the Superior Vena Cava During the Valsalva Maneuver in Normal Subjects

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The hemodynamic manifestations of the Valsalva maneuver are in part the result of changes in the venous return accompanying changes in intrathoracic pressure. Doppler echocardiography was performed during Valsalva maneuver in 13 normal subjects. Superior vena cava flow velocities and flow velocity integrals were measured in all 13 subjects. In the 5 subjects in whom the superior vena cava was clearly visualized throughout the maneuver, vena cava diameter was also analyzed. The superior vena cava flow velocity integral at rest was 17 ± 2 cm. It diminished significantly, disappeared or reversed (-13 ± 6 cm, $p < 0.001$) with phase I of the maneuver. During the maintenance phase (phase II), the flow velocity integral increased significantly (31 ± 2 cm, $p = 0.05$ vs baseline and phase I) and was associated with a decrease in superior vena cava lumen diameter at the time of Valsalva and continuing throughout the strain. With release of the maneuver (phase III), there was a sudden significant increase in flow velocity integral (61 ± 2 cm, $p = 0.005$ vs phase II) and superior vena cava lumen diameter. Subsequently, superior vena cava flow velocity integral returned to baseline values. This study suggests that one of the ways in which the Valsalva maneuver leads to decreased venous return may be by direct external compression of the superior vena cava.

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During the cardiovascular physical examination, latent physical findings can be augmented by simple maneuvers that alter flow dynamics through the heart and great vessels. One of the most extensively reviewed maneuvers is the Valsalva maneuver.^{1,2} The Valsalva maneuver, which consists of forceful exhalation against a closed glottis, causes a complex series of hemodynamic and heart rate changes. Although there have been several studies documenting the hemodynamic changes associated with the various stages of the maneuver, there has been less documentation of the changes in venous blood flow. Insofar as part of the proposed mechanism for the hemodynamic changes includes changes in venous return due to changes in intrathoracic pressure, evaluation of this parameter would be informative.

Doppler flow studies represent an easy, noninvasive means of evaluating flow phenomena.^{3,4} Local flow rates can be calculated by multiplying the Doppler-obtained flow velocity integral and the cross-sectional area of the vessel at the location of the sample volume. We attempted to study superior vena caval flow velocity in normal volunteers before, during and after a Valsalva maneuver and to try to apply these findings to the previously described changes.

METHODS

Valsalva maneuver was performed in 13 healthy volunteers (8 men, 5 women), between the ages of 27 and 32 years, with no previous history or findings of cardiovascular disease.

All echocardiographic studies were performed on an Interspec XL ultrasound instrument (Interspec, Inc.). All volunteers were placed in the recumbent position with the head flat or with the neck extended over a pillow. A 3.0- or 5.0-MHz transducer was positioned in the suprasternal or right supraclavicular fossa. The superior vena cava was visualized at the junction of the innominate and right subclavian veins and was confirmed by observation of the characteristic venous flow velocity pattern by Doppler examination (Figure 1). Measurements were performed during each phase of the Valsalva maneuver. The sample volume was electronically positioned within the superior vena cava to sample flows as close to the right atrium as possible. Flow velocity integrals were obtained by planimetry of the spectral analysis curve over a given cardiac cycle. Flow velocity integral determinations included all systolic and diastolic flow. Retrograde flows (i.e., flows di-

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TABLE I Heart Rate, Flow Velocity and Flow Velocity Integrals During the Various Phases of the Valsalva Maneuver

Phase	Heart Rate (beats/min)	p Value*	Peak Flow Velocity (cm/s)	p Value*	Flow Velocity Integral (cm)	p Value*
Baseline	67 ± 3		53 ± 3		17 ± 2	
I			-17 ± 2	<0.001	-13 ± 6	<0.001
IIA	64 ± 3	NS	56 ± 3	<0.001	28 ± 3	<0.005
IIB	74 ± 3	<0.05	63 ± 3	<0.05	31 ± 2	<0.05
III	79 ± 3	NS	98 ± 5	<0.001	61 ± 2	<0.005
IVA	89 ± 3	NS	48 ± 4	<0.001	16 ± 2	<0.005
IVB	62 ± 3	<0.005†	62 ± 3	†	26 ± 1	†

* All p values are compared to the previous phase except where indicated otherwise.

† Difference not significant vs baseline.

NS = not significant.

rected away from the heart and toward the transducer) were included in the calculations as negative areas (i.e., they were subtracted from the segment of the flow velocity integral that was directed toward the heart). Planimetry of the flow velocity curve and calculations of all flow velocity parameters were made on the Sony Cardiologic Analysis computer system, which is equipped with a digitizing tablet (Sony Medical Electronics Co.).

After establishing baseline Doppler flow velocity characteristics in the superior vena cava, we asked each volunteer to perform the Valsalva maneuver. Phase I was measured during the first 2 to 3 beats of the maneuver. Early straining (i.e., the subsequent 5 to 6 beats) was defined as phase IIA. The maneuver was maintained for approximately 30 seconds in each case. Late straining (the 3 to 4 beats immediately preceding

release of the strain) was defined as phase IIB. Release of the Valsalva was defined as phase III. The first 5 to 6 beats after the release of the Valsalva were defined as phase IVA. Ten to 20 seconds later, phase IVB was recorded. Superior vena caval flow velocity was monitored and recorded continuously by pulsed-wave Doppler from baseline until approximately 15 to 30 seconds after release of the maneuver.

When the maneuver was repeated on a given individual, baseline heart rate and flow parameters were re-established before repetition of the maneuver.

Heart rate, peak flow velocity and flow velocity integrals were expressed as mean ± 1 standard error of the mean. Differences in mean values were assessed using a paired Student *t* test.

RESULTS

Heart rate: The baseline heart rate was 67 ± 3 beats/min. There was no significant change in the heart rate during phase I of the maneuver (64 ± 3 beats/min). With continued strain (phase II), the heart rate increased significantly (74 ± 3 beats/min, $p < 0.01$). With release of the maneuver (phase III), the heart rate increased further (79 ± 3 beats/min). In the first few beats after release of the maneuver, the heart rate increased still further (phase IV) (89 ± 3 beats/min) but subsequently decreased (62 ± 3 beats/min) (Table I).

Doppler flow velocity measurements: **FLOW VELOCITY PATTERN AT BASELINE:** The baseline superior vena cava flow velocity pattern in each of the subjects was comparable to the flow velocity waves previously described by our laboratory³ and more recently confirmed by Appleton et al.⁴ A representative tracing is shown on the left side of Figure 1. Coinciding with the atrial kick (A

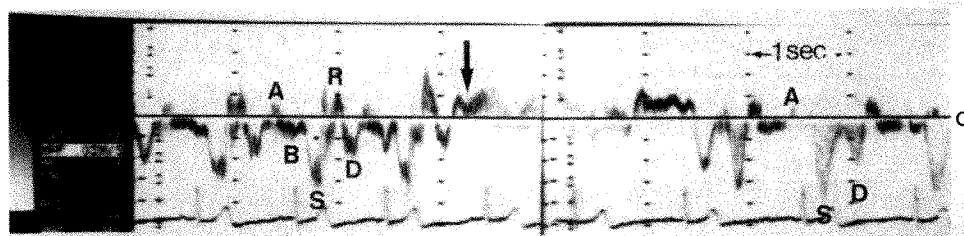


FIGURE 1. Superior vena cava flow velocity at the end of the baseline measurement and with the onset of the Valsalva maneuver (A, B, S, R and D wave explained in text). The arrow indicates the onset of the strain. There is a complete reversal (i.e., away from the heart) of flow that lasts for 2 cardiac cycles. 0 = zero line; the interval between the vertical velocity markers is 10 cm; 1-second intervals are also marked.

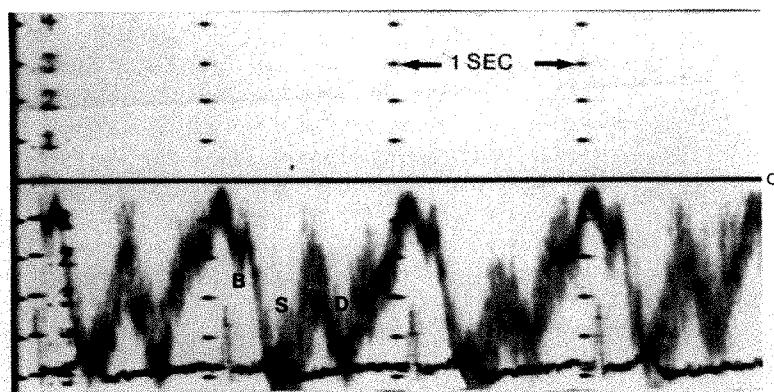


FIGURE 2. Superior vena cava flow velocity during the latter part of the strain (immediately preceding release of the strain). The peak flow velocity and flow velocity integral (calculated from the spectral analyses) are significantly higher than their respective baseline values. Flow is continuous and does not return to the zero line. Flow velocity and time markers as in Figure 1.

wave), there was a small retrograde flow velocity (away from the heart), after which flow velocity returned to the zero line transiently. This was followed by a small anterograde flow velocity (B wave), which corresponded to atrial relaxation after atrial systole. Subsequently, there was a large anterograde flow velocity (S wave), which represented atrial filling during ventricular systole and corresponds to the x descent on a central venous pressure tracing. Ventricular diastole was associated with another anterograde flow velocity wave pattern (D wave), which represented emptying of the right atrium when the tricuspid valve opened. Between the S and D waves, the flow velocity returned to the zero line. In 6 of the 13 volunteers, there was a small retrograde wave between the S and D waves (called an R wave by Cohen et al³). The baseline flow velocity integral was 17 ± 2 cm (systolic and diastolic flow velocity).

ONSET OF VALSALVA MANEUVER (PHASE I): With the onset of the maneuver, anterograde flow velocity decreased in 2 episodes, and became retrograde (i.e., flow velocity was directed away from the heart) in 11 episodes (as seen on the right side of Figure 1). This change persisted for approximately 2 cardiac cycles in all cases. The flow velocity integral during this part of the maneuver was -13 ± 6 cm. (Negative numbers indicate retrograde flow velocity, i.e., away from the heart.)

MAINTENANCE OF VALSALVA MANEUVER (PHASES IIA AND IIB): The flow velocity integral *increased* progressively throughout the maneuver and reached 31 ± 2 cm immediately before release of the strain (Figure 2). Although the flow velocity ceased at certain times during

the first few beats of the maneuver, flow during the latter beats of the maneuver became continuous. Nonetheless, as shown in Figure 2, the S and D waves were still easily distinguished.

RELEASE OF VALSALVA MANEUVER (PHASE III): With release of the maneuver, there was a further, sudden and significant increase in the flow velocity integral (61 ± 2 cm). There was a large anterograde wave noted that did not have the characteristic S and D waves seen during all other phases (Figure 3).

AFTER RELEASE OF MANEUVER (PHASES IVA AND IVB): The flow velocity integral returned to baseline values (16 ± 2 cm) within 7 seconds after release of the Valsalva maneuver (Figure 4).

The changes in peak flow velocity and flow velocity integral that occurred during each phase of the Valsalva maneuver are shown in Figures 5A and 5B, respectively.

SUPERIOR VENA CAVA DIAMETER: At the magnification used to accurately position the sample volume in the center of the vena cava, the resolution of the endothelial surface of the superior vena cava was difficult, and accurate measurements of superior vena cava diameter were not always possible. In 5 individuals, when the superior vena cava could be visualized throughout the Valsalva maneuver, there was a profound decrease and occasionally near total obliteration of the vessel lumen (in many cases it occurred immediately with the onset of the maneuver and resolved immediately after its release). In the 5 individuals with technically adequate images, the superior vena cava diameter diminished from 10 ± 3 mm at rest to 6 ± 2 mm during the maneuver (Figure 6A and 6B).

FIGURE 3. Superior vena cava flow velocity during the release of the strain. The solid arrow indicates the release of the strain. The flow velocity during the release exceeds the Nyquist limit in this subject, resulting in the phenomenon of aliasing on the spectral analysis (open arrow). Flow velocity and time markers as in Figure 1.

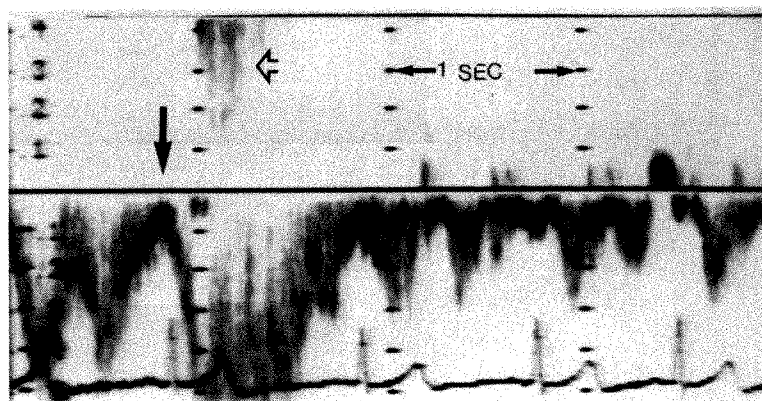
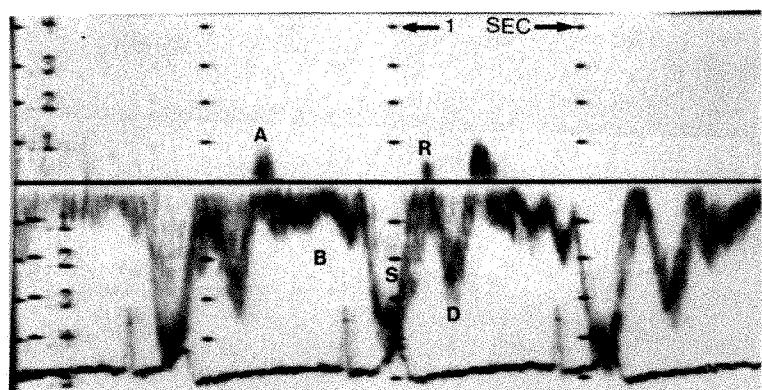


FIGURE 4. Superior vena cava flow velocity approximately 5 seconds after release of the maneuver. The flow velocity contour and magnitude has returned to near-baseline values. Flow velocity and time markers as in Figure 1.



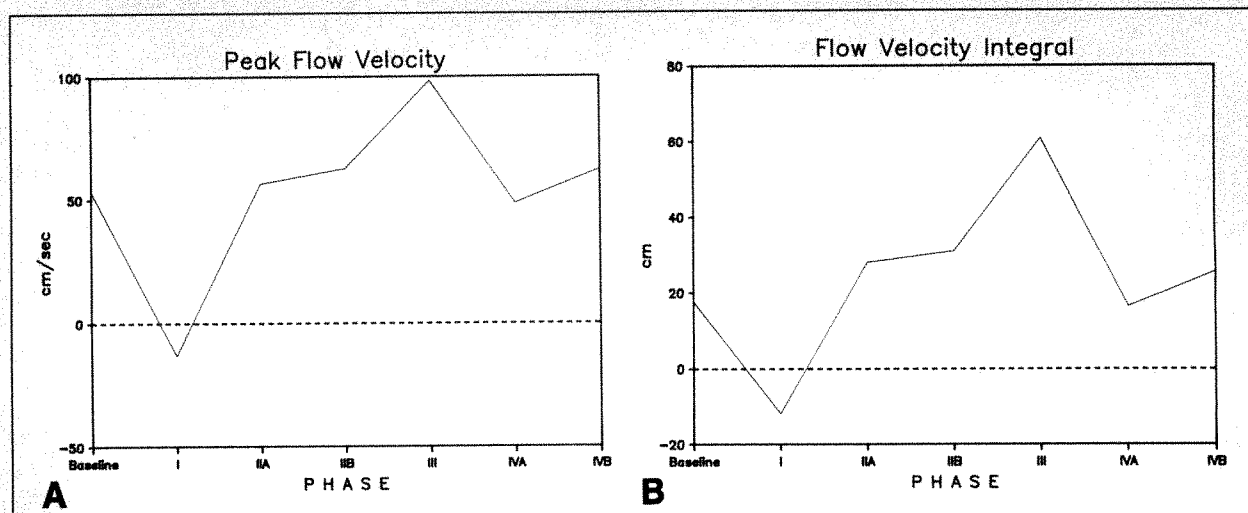


FIGURE 5. Peak flow velocity (A) and flow velocity integral (B) are shown during the baseline measurement and during each phase of the Valsalva maneuver. The data points represent the respective mean values at each phase. After the initial flow reversal seen in phase I, there is a progressive increase in both peak flow velocity and flow velocity integral. With release of the maneuver (phase III), the peak flow velocity and flow velocity integral increase further and subsequently return to baseline values.

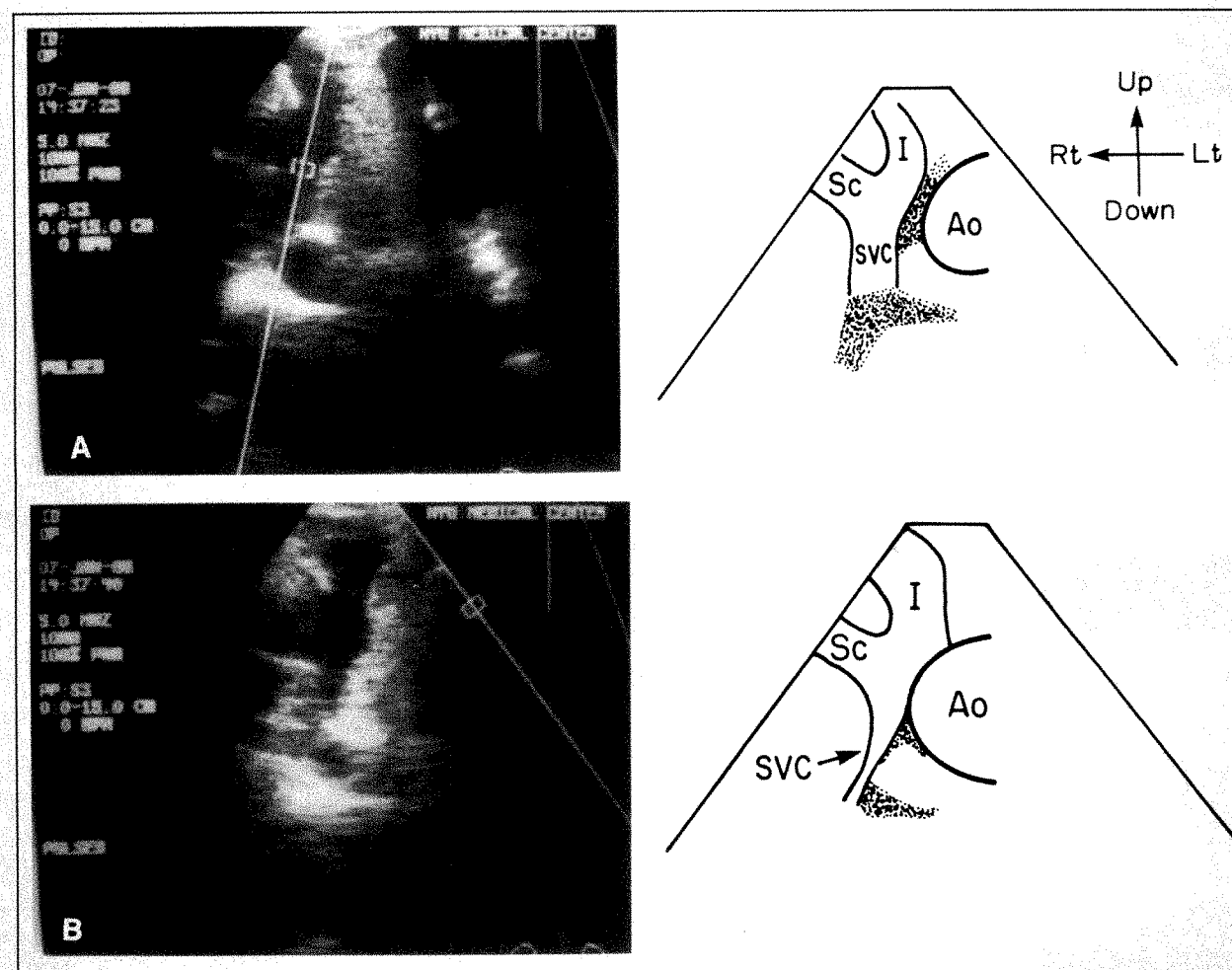


FIGURE 6. Views of the superior vena cava during baseline measurement (A) and just before release of the strain (B). The superior vena cava lumen has decreased markedly during the strain of the Valsalva maneuver. The Doppler sample volume has been moved to allow better visualization of the vessels. Ao = aorta; I = internal jugular vein; Sc = subclavian vein; SVC = superior vena cava.

DISCUSSION

To date, our understanding of the Valsalva maneuver has been based on studies involving blood pressure and heart rate monitoring during the maneuver. However, the underlying flow phenomena that represent the basis of the explanation of each phase have been less extensively studied and documented.

We evaluated the dynamics of central venous flow velocity during the Valsalva maneuver. During the initial phase of the strain, the flow velocity reversed. The acute increase in intrathoracic pressure associated with the strain without a concomitant increase in the pressure of the extrathoracic venous return explains this reversal of the normal flow pattern, which occurs during phase I. This increase in the intrathoracic pressure was associated with compression of the superior vena cava. As volume builds up in the extrathoracic veins, the pressure in these veins increases until forward flow is reestablished. Although the total flow through the superior vena cava decreases with maintenance of the maneuver, the flow velocity must increase to allow the volume to pass through the markedly diminished superior vena cava lumen. Therefore, the flow velocity integral increases significantly during phase II and remains elevated. In our study we divided the maintenance phase (phase II) into early and late stages. From this analysis we were able to show that the changes seen during this phase are progressive (i.e., the flow velocity integral increased from early phase II [IIA] to late phase II [IIB]). Upon release of the maneuver (phase III), there is a sudden significant decrease in the intrathoracic pressure. The superior vena cava lumen returns to its baseline diameter. Coincident with marked increase in lumen size is a decrease in superior vena cava pressure.

The increased pressure proximally in the extrathoracic vessels that had been necessary to maintain forward flow during the strain is now opposed by a significantly decreased intrathoracic pressure, leading to transiently higher flow rates during phase IV. The high flows into the superior vena cava during phase IV lead to a rapid equilibration of pressures and return to baseline flow dynamics. Monitoring of flow velocities immediately after release of the strain (phase IVA) and several seconds later (phase IVB) showed that the return to baseline occurred almost immediately and did not change significantly over the succeeding seconds.

This study noninvasively demonstrates the effect of the Valsalva maneuver on superior vena cava flow velocity and vessel size. It suggests that the decreased venous return noted during the strain of the maneuver is associated with increased flow velocity. Both the decreased flow and the increased flow velocity are, in part, due to compression and decrease in the diameter of the superior vena cava during the strain. The noninvasive nature of this study in normal volunteers did not allow invasive correlations. Studies are currently underway in our laboratory to determine the actual hemodynamic pressure correlates of the noninvasive observations made during this study.

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Real-Time Intravascular Ultrasound Imaging in Humans

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The capability of obtaining cross-sectional, high resolution images of arteries with the use of ultrasound catheters has recently been demonstrated in animal studies. In this study the in vivo feasibility of intravascular ultrasound imaging in humans was evaluated. In 26 patients who had undergone diagnostic cardiac catheterization or iliofemoral arteriography, 1 of 3 different models of 20-MHz ultrasound catheters was advanced retrograde, into the iliac arteries and aorta or antegrade into the femoral arteries and real-time cross-sectional images of the arteries were obtained in all. In 10, the iliac arteries were normal and appeared circular and pulsatile with a 3-layered wall and crisply defined lumens. In 7 patients with nonobstructive plaques, the plaque was easily identified in the ultrasound image as a linear, bright, adynamic echo-dense structure. In 4 with obstructive disease in the iliac artery, the arterial lumen appeared irregular, bordered by a thickened, nonpulsatile wall. Variable grades of atheromatous abnormalities in the wall could be visualized. In all 5 patients with arteriographic evidence of obstructive disease of the femoral artery, intravascular ultrasound displayed reduced lumens and irregular borders with protruding high-intensity echoes in the wall. In all patients, the arterial lumen and the normal or abnormal wall were well visualized in the ultrasound images. There were no complications. This study thus demonstrates the feasibility of intravascular ultrasound imaging of arterial circulation in humans. With further improvements in catheter design and image quality, this imaging approach is likely to have a number of potential applications in the assessment of peripheral and coronary arterial diseases and in guiding interventional therapeutic procedures.

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Selective arteriography, the standard method to evaluate coronary and peripheral arterial atherosclerosis, has limitations in providing precise assessment of obstructive arterial lesions.¹⁻³ Increased understanding of the diagnostic and prognostic importance of atherosclerotic lesions, and problems such as perforations and dissections encountered during catheter-based interventional procedures have emphasized the need for a technique that could delineate better the cross-sectional morphology of obstructive atherosclerotic arteries, particularly in the coronary arterial system.⁴⁻¹²

Among alternate attempts to derive this information, fiberoptic angioscopy has been found to be useful in yielding glimpses of the luminal surface of arteries, protruding atheromas, intravascular thrombi and intimal flaps.⁸ This technique, however, is cumbersome and does not allow precise assessment of the cross-sectional area, the size and composition of an atheroma or the thickness of the wall. Currently, considerable interest is focused on examining the potential of intravascular ultrasound catheters to obtain cross-sectional images of arteries and detect atheromas.¹³⁻²³ The capability of intravascular ultrasound imaging to yield real-time 2-dimensional images of peripheral, pulmonary and coronary arteries has been demonstrated in animals.^{13,18-23} This study explores the in vivo feasibility of intravascular high frequency ultrasound imaging of the arterial system in conscious humans.

METHODS

Intravascular ultrasound imaging devices: We used 3 different models of intravascular ultrasound imaging catheters. In all models, the probe is designed to be inserted into an artery via an introducer sheath. In 13 patients, a prototype intravascular imaging instrument (Summit Technology) was used, the details of which have been described previously.¹³ This device is 120 cm long and consists of an outer 6Fr probe sheath and an inner moving probe core with a single 20-MHz ultrasound transducer tip. During operation the probe core and transducer are rotated mechanically at 1,800 revolutions/min within the stationary sheath. The image, transmitted to a calibrated display system in real-time, has a resolution of 0.25 mm. In 12 patients, we used a commercially available, intravascular ultrasound probe (Sonicath, Boston Scientific Corp.). This device is a 6Fr disposable catheter enclosing a mechanically rotating driveshaft with a 20-MHz ultrasound crystal at its tip. The catheter is used with an imaging console adapted for 20-MHz use and 3,600 scans (Diasonics). The cath-

eter has tracts for guidewires, a proximal tract at the distal end of the catheter and a distal tract protruding beyond the catheter tip. In 1 patient, we used another commercially available ultrasound catheter, containing a 20-MHz fixed crystal and a rotating mirror (Cardiovascular Imaging Systems).¹⁴

Intravascular ultrasound imaging: We studied 26 patients after obtaining informed consent and with the approval of the institutional human investigation review committee. Intravascular imaging of the abdominal aorta and iliac arteries was performed in 19 patients after clinically indicated diagnostic cardiac catheterization for coronary artery disease. The presence and location of atherosclerotic lesions was evaluated by angiography as well. In 7 patients who underwent iliofemoral arteriography for peripheral vascular disease, intravascular imaging of the iliac arteries was performed in 2 and of the femoral arteries in 5. After the diagnostic procedure in each group, a 7Fr introducer sheath was placed in the femoral artery. Then, under fluoroscopy, the ultrasound catheter was advanced retrograde into the iliac artery to the level of abdominal aorta, or antegrade into the femoral artery (Figure 1). From the time of introduction of the ultrasound catheter, ultrasound images were continuously recorded on videotape. Whenever the ultrasound images appeared to show abnormalities, the intravascular location of the catheter was noted by fluoroscopy. After imaging was completed, the ultrasound catheter and the sheath were removed and hemostasis achieved.

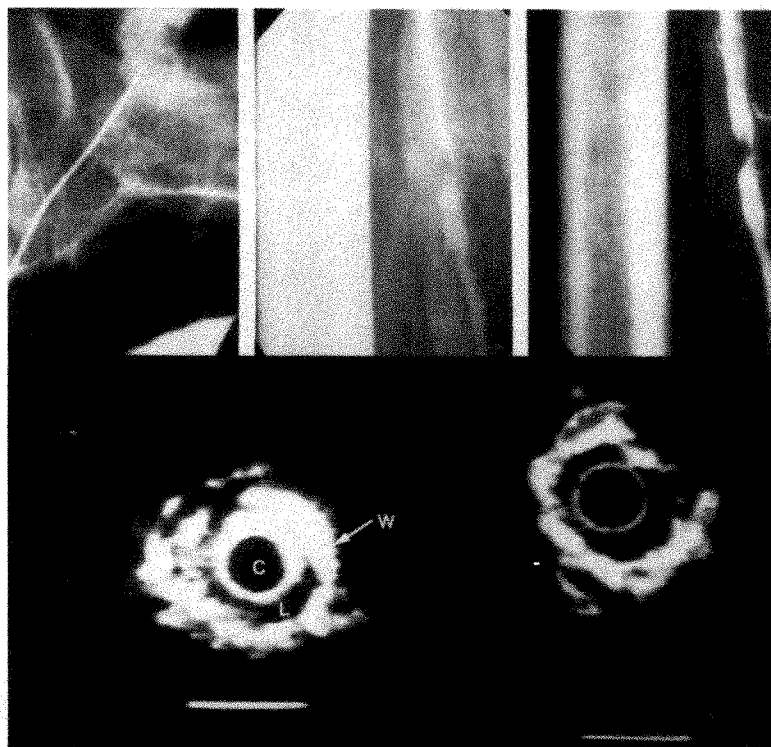
RESULTS

Among the 26 patients, contrast angiography showed normal iliac arteries in 10, nonobstructive plaques with or without calcification in the right iliac

artery in 7, moderately obstructive disease in the right iliac artery in 2, severe obstructive disease in both iliac arteries in 2 and severe to mild degrees of obstructive disease in the femoral arteries in 5.

In all 26 patients, intravascular ultrasound yielded dynamic cross-sectional images of the arteries in real-time (Figures 1 to 5). Perfectly circular and pulsatile images of the normal iliac arteries were obtained in 8 of the 10 patients who evidenced no abnormalities in the contrast angiogram (Figures 2 and 3). The catheter tended often to align with one area of the wall but it could be manipulated to the center of the vessel for brief periods. Except during imaging of the abdominal aorta, the whole circumference of which was beyond the range of ultrasound depth resolution in some, we were able to obtain circular images in all circumstances. The pulsatile nature and the changing caliber of the vessel could be easily appreciated as the catheter was advanced in various arteries. In the patients in whom we used the prototype device, we could not visualize the arterial wall thickness clearly in most. In the images obtained with the refined ultrasound catheters used in later patients, the wall definition and resolution were superior. Normal iliac and femoral arteries appeared with a 3-layered appearance of the wall consisting of a thin inner echogenic layer, a middle hypoechoic layer and an outer echobright layer (Figures 3, 4A). Even when the outer layer blended with the signals arising from adjacent structures, the pulsatile nature of the vessel and optimum adjustment of the technical controls allowed recognition of the outer boundary of the wall. Two patients with normal angiographic anatomy exhibited increased focal thickening of the inner layer in the ultrasound images (Figure 4B). In patients with calcific plaques, an intense echodensity was noted at 1 or multiple segments of the

FIGURE 1. Radiographic images showing the ultrasound catheter and intravascular ultrasound images obtained with a prototype catheter. *Top left*, ultrasound catheter in the right iliac artery of a patient. *Top middle*, ultrasound catheter in the femoral artery of another patient. *Top right*, femoral arteriogram of the same patient depicting severe stenosis. *Bottom left*, ultrasound image recorded at a stenotic site in the femoral artery from the patient whose arteriogram is shown. The lumen (L) size is small and the wall (W) exhibits irregular thickness and high intensity echoes. *Bottom right*, ultrasound image of a diseased iliac artery from another patient, showing an irregularly shaped lumen. The white bar represents a 5-mm calibration mark. C = catheter signal.



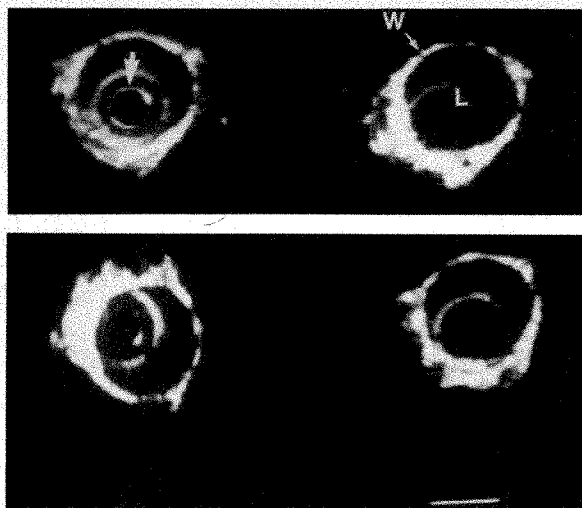


FIGURE 2. Intravascular ultrasound images of normal iliac arteries obtained with the prototype ultrasound device, from 4 patients. The white bar represents a 5-mm calibration mark. The small circles (arrow, top left) seen inside the arterial lumens (L) are catheter ring signals. The arteries appear circular with crisply defined lumens. The catheter tends to align to 1 side of the wall (W).

vessel (Figure 5). This echodensity exhibited no pulsation while the other portions of the artery at the same cross-sectional level were dynamic. While the arterial wall could be seen for the most part at this site, the wall segment outlying calcific plaques was not visualized owing to signal attenuation by the calcium. In the 2 pa-

tients with moderately obstructive iliac disease seen on angiography, the ultrasound image revealed a smaller lumen with an irregular, nonpulsatile wall (Figures 1 and 4). In one, a linear free-edged structure, consistent with an intimal flap, was seen oscillating within the lumen (Figure 4D). In the 2 patients with severe obstructive disease of the iliac arteries, striking reductions in the area and marked alterations in the shape of the lumen were noted at various segments (Figure 5). The inner layer of the vessel wall was markedly thick, filled with both soft echo signals and focally bright areas. The degree of inner layer thickness was highly variable at different radii of the cross-sectional image and at different levels of the vessel. The middle layer appeared thinner or indistinct at sites of severe disease. In all the 5 patients who manifested disease in the femoral arteriogram, the intravascular ultrasound images were abnormal. The lumens were irregularly shaped, bordered frequently by high intensity bright echo signals (Figure 1).

There were no complications related to intravascular ultrasound imaging or the diagnostic procedure in any of the patients. The patients did not feel any unusual sensation or discomfort with intravascular ultrasound imaging. The catheter demonstrated no clots or damage after removal.

DISCUSSION

Our experience indicates that in vivo intravascular ultrasound imaging of arterial circulation is feasible in humans and that it has the ability to differentiate diseased arteries from normal vessels. The ability to image

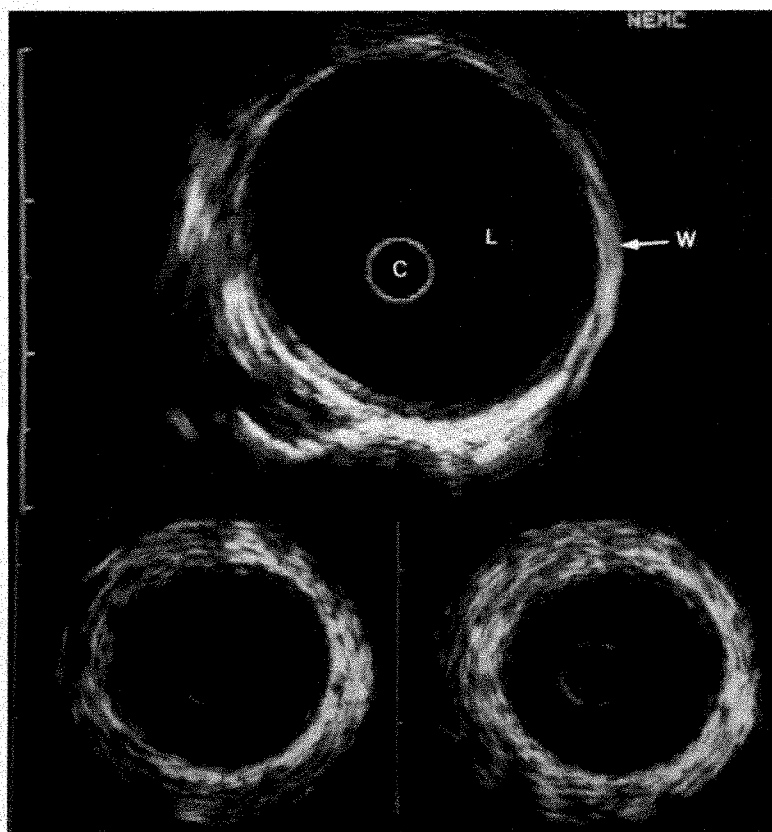


FIGURE 3. Intravascular ultrasound images (obtained with a newer intravascular ultrasound catheter containing a 20-MHz rotating crystal), of the abdominal aorta (top), and iliac arteries (bottom) from 3 patients with angiographically normal vessels. The distance between the closest calibration marks is 5 mm. C = catheter signal; L = lumen; W = wall.

FIGURE 4. Intravascular ultrasound images (obtained with a newer intravascular ultrasound catheter containing a 20-MHz rotating crystal) from 4 different patients. **A**, iliac artery from a patient with normal angiogram. **B**, iliac artery from a patient with normal angiogram shows unevenly thickened inner layer with atheromatous plaques. **C**, iliac artery from a patient with moderately obstructive disease on the angiogram. The wall presents a three layered appearance. The inner wall layer is thickened to a greater degree than in a normal artery. **D**, 2 different frames of an iliac artery from a patient showing an oscillating linear intimal flap. (C = catheter signal; L = lumen; W = wall; F = flap.) The distance between the closest calibration marks is 5 mm.

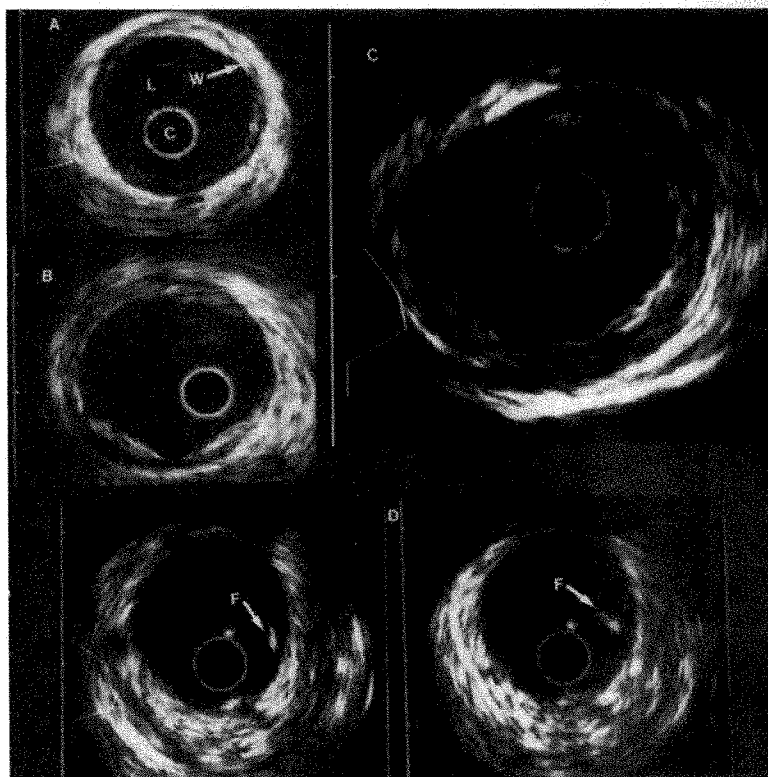
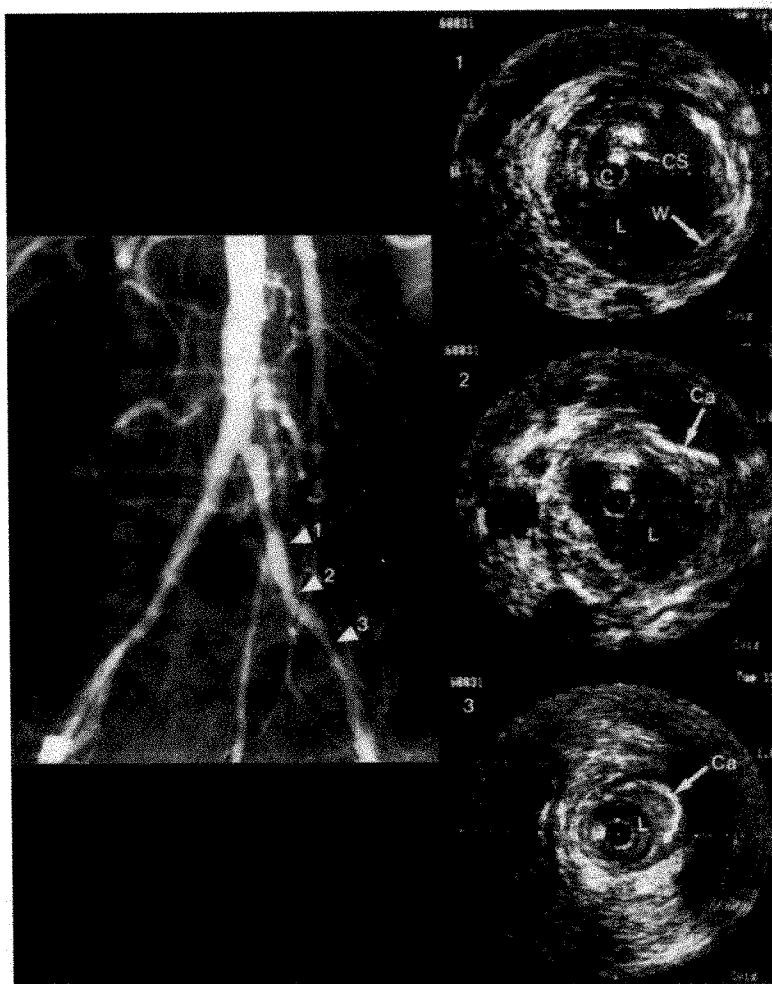


FIGURE 5. Arteriogram and intravascular ultrasound images (obtained with a 20-MHz fixed-crystal/rotating mirror device), of the left iliac artery from a patient with significant obstructive disease. The arrows point to the sites of ultrasound imaging. The lumen size corresponds to the angiographic narrowing. The varying luminal shape is well evident. The outer portion of the wall is not seen at sites of calcification because of signal attenuation. The distance between the closest calibration marks is 1 mm. C = catheter signal; Ca = calcific plaque; CS = catheter strut signal; L = lumen; W = wall.



a pulsatile artery in its cross-section in real-time provides a unique strength to the diagnostic and therapeutic approach for arterial diseases. The importance of the cross-sectional anatomy of an atherosclerotic vessel—the luminal shape and size, the morphology of an atheroma and the thickness of the arterial wall—is being increasingly recognized in assessing the clinical significance of an arterial stenosis⁵⁻⁸ and when attempting catheter-based interventional procedures.⁹⁻¹² The tendency of interventional catheter devices to slip away from fibrocalcific atheromas and engage the points of least resistance often result both in incomplete removal of obstructions, and in complications such as perforations and arterial dissections. Adequate visualization of the lumen, obstructive atheroma and the vessel wall thickness during interventional procedures could aid in directing the interventional device to the precise target site, and in deciding when to quit and when to persist. Intravascular ultrasound imaging appears to have the potential to provide needed guidance.¹⁷⁻²³ Ability to measure lumen area and wall thickness by intravascular ultrasound and to detect atheromas, arterial dissections and intraluminal thrombi has been demonstrated in vitro.¹⁵⁻²¹ In vivo studies in animals and preliminary experience in humans point to the capability of obtaining real-time images of various blood vessels, including coronary arteries, and of identifying intimal flaps and intravascular thrombi.^{13,14,18-23}

Our study extends the previous in vitro and in vivo animal work to humans. Since our attempt was only to assess the feasibility, we did not perform systematic quantitative comparisons between intravascular ultrasound and arteriography. Our experience also points out certain problems that need to be addressed before this type of catheter-based ultrasound imaging is extended to make routine diagnostic or therapeutic decisions. While in vitro experiments have yielded high resolution images of the wall, such definition of the arterial wall appears to be difficult to obtain consistently in vivo. Since the catheter often tends to align to one side of the wall, constant fine manipulation appears to be necessary to get circular images with good resolution. How well the catheter can be negotiated in tortuous vessels and in highly mobile coronary arteries remains to be examined. While the lumen is depicted well in general, the presence of fibrocalcific plaques appears to attenuate the ultrasound signal strength, making it difficult to recognize the wall outlying a plaque. With future improvements in catheter design and image processing, these problems are likely to be solved. Further refinements in instrumentation, and systematic in vivo human investigations, are necessary to verify the ability of intravascular ultrasound in quantitating the size and composition of an atheroma, in guiding interventional procedures, in assessing the effects of interventions and in defining the practical utility in coronary circulation.²³

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Suppression of Ventricular Arrhythmias by Magnesium

Dan Tzivoni, MD, and Andre Keren, MD

Magnesium (Mg) is an essential activator of sodium potassium adenosine triphosphatase, and thus has an important role in maintaining the resting membrane potential, which depends on intraextracellular potassium gradient.^{1,2} Mg deficiency is associated with loss of intracellular potassium, increase in intracellular sodium and augmentation of cell excitability.^{1,3} The increased intracellular sodium is followed by sodium-calcium exchange, which favors transient depolarizations and repetitive arrhythmias.⁴ Infusion of Mg sulfate at different rates of atrial pacing did not affect blood pressure, PR, QRS or QT intervals.⁵ Mg infusion in man caused only minimal electrophysiologic changes in atrial and AV junctional tissue, while there was no significant change in ventricular parameters.⁶ Despite these modest electrophysiologic effects, Mg proved to be an effective antiarrhythmic agent in certain clinical conditions.

CONDITIONS ASSOCIATED WITH HYPOMAGNESEMIA

The recommended daily allowance of Mg for a healthy adult is 5 mg/kg.⁷ In elderly patients or patients with intestinal absorption disorders, the dietary intake is reduced and therefore they are more prone to develop hypomagnesemia.⁸

Hypomagnesemia is frequent in patients receiving long-term diuretic therapy. The use of loop diuretics and thiazides is associated with increased urinary excretion of Mg. Low Mg levels were found in 37% of patients with congestive heart failure who were receiving diuretics.⁹ A high percentage (38 to 42%) of patients receiving diuretic therapy with hypokalemia also have hypomagnesemia.^{9,10} While potassium depletion is usually corrected by most physicians, replacement of Mg is usually neglected. Even in the presence of normal Mg levels, the myocardial cells may be depleted of magnesium.¹¹

MAGNESIUM AND VENTRICULAR ARRHYTHMIAS

The association between low Mg levels and increased cardiac mortality has been noted by several investigators. Chipperfield and Chipperfield¹² found low myocardial Mg levels in cases of sudden cardiac death. Johnson et al¹³ found that the Mg level was low in sudden death patients who had a history of angina pectoris.

Epidemiologic data suggest an association between sudden death and low Mg in the soil or in the water supply.¹⁴⁻¹⁶ Increased ventricular ectopic activity was reported in patients receiving long-term diuretic therapy.^{17,18} Potassium replacement in these patients did not increase the intracellular level of potassium and did not reduce the frequency of ventricular arrhythmias.¹⁷ Administration of Mg sulfate caused an increase in cellular potassium content and decreased the frequency of arrhythmias. Mg deficiency causes depletion of muscle potassium,³ which can persist despite large intake of potassium. It seems, therefore, that the ability to maintain the potassium gradient is dependent on the presence of Mg. Several large-scale studies have indicated increased mortality and sudden death rates in hypertensive patients receiving long-term diuretic therapy.¹⁹⁻²¹ Lown et al²² found hypokalemia-related arrhythmias in 24% of patients with sudden cardiac death who were receiving diuretic therapy.

DIGITALIS TOXICITY

Ventricular arrhythmias induced by digitalis toxicity are very sensitive to Mg therapy. Mg can suppress ventricular arrhythmias in patients with both normal Mg levels and hypomagnesemia, which is common in patients with digitalis toxicity.^{23,24} Hypomagnesemia is more common than hypokalemia during digitalis toxicity²⁴ and, even in the presence of normal serum Mg levels, its intracellular level in lymphocytes is frequently low.²⁵ Therefore, potassium replacement in these patients is not sufficient and has to be accompanied by administration of Mg. Mg counteracts the inhibitory effect of digitalis on sodium potassium adenosine triphosphatase. During digitalis therapy there is an increase in intracellular calcium, leading to augmentation of inotropism and excitability.²⁶ In experimental animals deprived of Mg, decreased tolerance to digitalis was reported²⁷ and the duration of digitalis toxicity was more prolonged.²⁸ Therefore, Mg levels should be determined routinely in patients receiving digitalis therapy and intravenous Mg should be part of routine treatment of patients with digitalis toxicity who have ventricular arrhythmias.

TORSADE DE POINTES

Torsade de pointes is a life-threatening ventricular arrhythmia in which treatment with Mg has recently been proven to be very effective. This repetitive polymorphous ventricular tachycardia occurs in the presence of QT prolongation^{29,30} most commonly induced by type Ia antiarrhythmic drugs, such as quinidine or disopyramide.^{29,31,32} Other QT-prolonging drugs, such as amiodarone,³³ procainamide³⁴ and psychotropic

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drugs,³⁵ have also been reported to induce this arrhythmia. Bradycardia, hypokalemia and hypomagnesemia can increase the likelihood of developing torsade de pointes and in rare cases can be its only cause.^{29,36,37} Standard treatment of torsade de pointes is aimed at shortening the prolonged and dispersed repolarization. This can be achieved by accelerating the heart rate either by isoproterenol infusion^{29,38} or by cardiac pacing.^{29,37,39} Isoproterenol is contraindicated in patients with acute infarct, angina pectoris or hypertension, and, if given erroneously to a patient with ventricular tachycardia that is not torsade de pointes, it may lead to a fatal outcome. Both atrial and ventricular cardiac pacing are safe and effective modalities in the treatment of torsade de pointes. Cardiac pacing, however, requires skilled personnel and equipment and therefore cannot be applied rapidly in every ambulance or emergency room where the arrhythmia is encountered.

We introduced Mg sulfate as a new method for the treatment of torsade de pointes.^{40,41} Intravenous Mg sulfate was effective in all 12 consecutive patients in whom it was tried. In 9 patients a single bolus of 2 g of Mg sulfate completely abolished torsade de pointes within 2 to 5 minutes. In the other 3, a second bolus of 2 to 4 g was given 5 to 15 minutes later, leading to suppression of the torsade de pointes and the ventricular premature beats. In 9 of the patients, continuous infusion of 3 to 20 mg/min of Mg sulfate was given for 7 to 48 hours until the QT regressed below 0.50 second. Although the response to Mg was prompt, it did not cause immediate shortening of the QT interval. Mg levels were normal in all 8 patients in whom it was available, while potassium levels were below 3.5 mEq/liter in 8 of the 12 patients. Since our last report⁴¹ we successfully treated 3 more patients with torsade de pointes using Mg. Similar findings were reported by Perticone et al,⁴² while a less favorable response was reported in 1 case by Toivonen and Leinonen.⁴³ The administration of Mg, in our experience, was not accompanied by any significant side effect except for a short-lasting flushing sensation. The advantages of Mg therapy over the other therapeutic modalities are obvious. It can be administered rapidly whenever the diagnosis of torsade de pointes is made. Mg can be applied by any medical personnel, the response is very prompt and its use is free of side effects. If given to a patient with a ventricular tachycardia that is not torsade de pointes, it may not suppress it,⁴⁴ but no deleterious response is expected. It seems, therefore, that intravenous Mg should be the treatment of choice in torsade de pointes.

Bailie et al⁴⁵ produced QT prolongation in experimental animals using cesium chloride. This was associated with the appearance of early after-depolarizations and ventricular arrhythmias resembling torsade de pointes. Mg administration suppressed the early after-depolarization and the torsade de pointes without shortening the QT interval. Thus, the investigators believe that the mechanism of this arrhythmia is triggered activity and that Mg abolished the torsade de pointes by suppressing early after-depolarizations. Davidenko et al⁴⁶ used quinidine to produce prolongation of the action potential, early after-depolarization and triggered activ-

ity in canine Purkinje fibers, conditions known to predispose the development of torsade de pointes; all these changes were suppressed by Mg.

ACUTE MYOCARDIAL INFARCTION

In acute myocardial infarction several studies have indicated a transient decrease in serum Mg level.⁴⁷ Speich et al⁴⁸ found low Mg levels in the infarcted areas along with high levels of calcium and low levels of potassium. Rector et al⁴⁹ found normal Mg levels in patients with uncomplicated infarct, while patients with acute infarct and complicated ventricular arrhythmia and those with congestive heart failure had low Mg levels. An increase in the frequency of ventricular ectopic activity among 342 patients with acute myocardial infarction and hypomagnesemia was reported by Dyckner.⁵⁰ The mechanism of hypomagnesemia in patients with acute myocardial infarction is not clear. Flink et al⁵¹ studied 16 patients with acute myocardial infarct. They found high fatty acid and low Mg levels during the acute phase of the infarct. During the following 3 days, the levels of the free fatty acids and Mg returned to normal. It is probable that the reduced Mg level was due to its sequestration with the free fatty acids.

The effect of supplementation of Mg chloride in patients with acute infarct was studied by Abraham et al.⁵² These investigators found that in patients with acute infarct a single bolus of Mg sulfate reduced the frequency of ventricular arrhythmias from 35 to 15% in the following 4 hours. The investigators therefore advocate the routine administration of Mg to patients with acute myocardial infarction.

We recommend routine determination of Mg levels in patients with a high likelihood of hypomagnesemia, such as those with congestive heart failure receiving diuretic therapy, especially if they are elderly. While in the past Mg supplement was available only in the intravenous form of Mg sulfate, an enteric-coated Mg chloride preparation has recently been introduced that is well tolerated. Mg chloride should be given to patients when hypomagnesemia is detected. It is probable that even in the presence of normal magnesium levels many patients require Mg supplementation as they may have low intracellular levels of magnesium. In other groups, such as patients with digitalis toxicity, torsade de pointes or complicated acute myocardial infarction, Mg chloride administration is recommended regardless of blood Mg levels. It is reasonable to assume that most patients who require potassium supplement also require addition of magnesium. For this reason our opinion is that there is a need for a new oral preparation containing both potassium and magnesium.

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Effects of Ventricular Pacing on Atrial Natriuretic Peptide Levels During Submaximal Exercise in Complete Atrioventricular Block

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Atrial natriuretic peptide (ANP) is a peptide with natriuretic, diuretic and vasodilatory properties in animals and humans. Most investigators report a progressive increase in ANP during exercise with significantly higher ANP levels even during submaximal exercise¹⁻⁴; factors found to be correlated with ANP levels are workload¹⁻⁴ and ventricular rate.²⁻⁴ However, a recent study described static ANP levels despite maximal exercise⁵; the discrepancy was suggested to be related to the difference in the ventricular rate achieved.⁵ Also, an animal study reported a proportional increase in ANP prohormones to incremental right ventricular pacing while atrial pressure decreased concomitantly,⁶ suggesting a direct relation of ANP to ventricular rate independent of atrial pressure. To discern the relation between ANP secretion, exercise, ventricular rate (independent of atrial rate) and hemodynamic performance, we studied the ANP levels in patients with complete atrioventricular (AV) block on rate-responsive ventricular pacemakers during submaximal exercise.

Five patients (mean age 60 years, range 32 to 72) with complete AV block on minute ventilation-sensing Meta pacemakers (Telectronic-Cordis) volunteered for the study and gave informed consent. One was subsequently excluded because of resumption of AV conduction during exercise. All patients had normal left ventricular dimensions and systolic function on the 2-dimensional echocardiogram and none had ischemic heart disease. Retrograde AV conduction was absent in all patients. All were initially familiarized with exercise on a cycle ergometer. The exercise program started at a work level of 10 watts and increased by 10 watts every 2 minutes for 12 minutes (i.e., maximum workload of 60 watts). We performed continuous-wave Doppler cardiac output assessment during exercise using a Doppler ultrasound unit (Exerdop, Quinton), with a transducer placed at the suprasternal notch. The minute distance is the product of the heart rate and the stroke distance measured. The peak velocity and the peak acceleration of blood flow during systole were also computed by the Doppler unit. Two exercise tests were performed for each patient, first in the VVI mode and then in the rate-responsive mode. The patient was blinded to the pacing mode. There was a 2-hour rest between the 2 exercise tests. We set an arterial line to monitor blood pressure and to draw blood for ANP levels every 3 minutes during exercise and, subsequently, at 1.5, 3, 6, 9 and 15 minutes of the recovery period. Plasma was separated at 4°C and stored at

-20°C. All plasma samples were extracted using Sep-pak C18 cartridges before radioimmunoassay, which used labels from Amersham International. We measured all samples from any 1 patient in a single radioimmunoassay run. The coefficient of variation within assay was 8%. Hemodynamic recordings, including heart rate, blood pressure and Doppler assessment, were made by another physician at the same time as the drawing of blood. Results were expressed as mean $\pm$ standard error of the mean. Comparison was made between results obtained at baseline and results obtained at each blood sampling using the Student *t* test. A *p* value <0.05 was considered significant.

With VVI pacing at 70 beats/min, the ANP level was steady throughout the exercise and recovery period (baseline ANP level 57 ± 17 pg/ml, peak ANP level 62 ± 20 pg/ml) despite a significant increase of minute distance, peak acceleration and velocity of ascending aortic blood flow (Table I). In the rate-responsive mode, all patients achieved similar degrees of change of the pacing rate and the other hemodynamic parameters measured during exercise. The pacing rate increased from the baseline of 70 beats/min to 140 ± 6 beats/min ($p < 0.01$). We noted an increase in ANP level from 59 ± 16 to 88 ± 24 pg/ml but this failed to reach statistical significance (Table I). Analysis of individual data revealed that rate modulation during exercise increased ANP level in only half of the patients.

There have been scanty data on the ANP level of pacemaker-dependent patients during maximal exercise⁷ and no study on ANP levels during submaximal exercise has been performed. Atrial pressure during exercise has not been studied in all previous reports,^{1-5,7} although a high atrial pressure was suggested to explain the high ANP levels with exercise.^{1,2,4,7} With fixed-rate VVI pacing, right atrial pressure increased during exercise.⁸ Thus, our finding of a constant ANP level during incremental exercise argued against the dominant role of the atrial pressure alone to modulate ANP secretion during exercise. Recent studies of changes in ANP levels after relief of cardiac tamponade or constriction^{9,10} suggested atrial transmural pressure and atrial stretch, rather than atrial pressure, as the actual ANP stimulus. The atrial transmural pressure is a function of both the intraatrial pressure and the intrapericardial pressure. We have no data on its changes with exercise in our patients, but it is possible that a simultaneous increase in intrapericardial pressure with exercise during VVI pacing would result in a static atrial transmural pressure and hence static atrial stretch and ANP levels. Also, with VVI pacing, all the patients had significant increases of the stroke distance, peak aortic acceleration and velocity, reflecting increased cardiac contractility. Thus, ANP levels during exercise were not correlated with contractility. With ventricular

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TABLE I Atrial Natriuretic Peptide Levels and Hemodynamic Findings During Submaximal Exercise in the VVI Mode and the Rate-Responsive (RR) Mode

	Exercise					Recovery				
Time (minutes)	0	3	6	9	12	1.5	3	6	9	15
Patient										
1										
VVI ANP	19	22	16	20	19	14	18	14	33	30
RR ANP	18	18	20	19	36	18	27	24	25	42
2										
VVI ANP	38	41	34	37	60	32	46	40	48	44
RR ANP	48	50	68	90	98	71	43	40	33	33
3										
VVI ANP	90	58	74	85	85	87	114	115	95	91
RR ANP	88	81	65	54	75	87	112	92	70	36
4										
VVI ANP	82	79	55	71	64	68	68	63	36	32
RR ANP	80	68	88	127	147	137	114	127	46	37
Mean value VVI										
ANP	57 ± 17		45 ± 13		58 ± 11		62 ± 20		49 ± 14	
HR	70		70		70		70		70	
MD	574 ± 144		915 ± 235*		921 ± 225*		744 ± 219*		588 ± 144	
Pka	12 ± 2		19 ± 3*		23 ± 5*		18 ± 4†		12 ± 2	
Pkv	0.53 ± 0.09		0.79 ± 0.16*		0.79 ± 0.13*		0.68 ± 0.16†		0.55 ± 0.1	
MBP	89 ± 2		108 ± 9†		113 ± 8†		99 ± 4		84 ± 2	
Mean value RR										
ANP	59 ± 16		60 ± 14		88 ± 24		74 ± 23		37 ± 2	
HR	70		131 ± 7*		140 ± 6*		94 ± 8*		70	
MD	644 ± 156		876 ± 224*		1097 ± 247*		896 ± 295*		675 ± 181	
Pka	15 ± 2		16 ± 3		20 ± 3†		19 ± 3†		15 ± 3	
Pkv	0.58 ± 0.07		0.64 ± 0.12		0.68 ± 0.13		0.71 ± 0.15		0.62 ± 0.1	
MBP	100 ± 4		112 ± 4		120 ± 4†		105 ± 2		98 ± 3	
ANP = atrial natriuretic peptide; HR = heart rate; MD = minute distance; MBP = mean blood pressure; Pka = peak acceleration of aortic flow; Pkv = peak velocity of aortic flow.										

ANP = atrial natriuretic peptide; HR = heart rate; MD = minute distance; MBP = mean blood pressure; Pka = peak acceleration of aortic flow; Pkv = peak velocity of aortic flow.

rate modulation, half of our patients showed a change in ANP secretion with increasing levels during incremental exercise and half showed a similar ANP profile to VVI pacing, suggesting that a proper ventricular rate response allowed ANP secretion but was insufficient to trigger ANP release. Rate-responsive pacing, in addition to its well-proven hemodynamic benefits over VVI pacing, also appears to confer the metabolic advantage of a more physiologic ANP profile with submaximal exercise.

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HLA-A, B, DR, and DQ Antigens in Black Patients with Idiopathic Dilated Cardiomyopathy

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The HLA antigens, which are encoded by closely arranged genes on the short arm of the sixth chromosome, influence the predisposition to several diseases.¹ Some with initially weak associations with HLA-A and HLA-B antigens have been found to have stronger associations with HLA-DR antigens.² Since a genetic predisposition to the development of idiopathic dilated cardiomyopathy has been postulated, and since there is little information on the relation between antigens at the DR and DQ loci of the HLA system and idiopathic dilated cardiomyopathy,³⁻⁵ we performed HLA typing in a group of

black patients with this disease to determine if immunogenetic factors could be involved in the pathogenesis of idiopathic dilated cardiomyopathy.

HLA-A and HLA-B typing was carried out in 62 black patients with idiopathic dilated cardiomyopathy who had been admitted and evaluated at King Edward VIII Hospital, Durban, and HLA-DR and HLA-DQ typing was performed in 57 of these individuals; all had evidence of global hypokinesis on echocardiography. None had any disease other than idiopathic dilated cardiomyopathy; habitual alcoholics and hypertensives were excluded. Coronary angiography was not performed in any of the patients because coronary artery disease is rare in the black population of South Africa.^{6,7} Patients were aged between 17 and 63 years. The control group consisted of 1,416 normal adults for the HLA-A and HLA-B typing, 220 for the HLA-DR typing and 198 for the HLA-DQ typing. Although over 2,000 individuals have been tested for the HLA-DQ locus in our laboratory, the majority were caucasoid or patients with

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TABLE I Frequencies of HLA-A Antigens (%)

Antigen	Pts (n = 62)	Control Subjects (n = 1,416)
A1	11.3	6.4
A2	27.4	21.4
A3	16.1	12.6
A11	0.0	0.1
A23	12.9	18.3
A24	3.2	4.9
A25/34	14.5	13.5
A26	9.7	10.5
A28	19.4	20.9
A29	12.9	17.1
A30	35.5	37.4
A31	4.8	6.0
A32	3.2	2.3*
Aw33	8.1	2.2
One antigen	21.0	26.4

Difference not significant for all comparisons.
* Uncorrected p < 0.005.

TABLE III Frequencies of HLA-DR Antigens (%)

Antigen	Pts (n = 57)	Control Subjects (n = 412)	p Value	Corrected p Value
DR1	12.3	4.6	<0.025	NS
DR2	29.8	24.0	NS	NS
DR3	28.1	36.2	NS	NS
DR4	7.0	10.0	NS	NS
DR5	38.6	35.2	NS	NS
DRw6	24.6	14.6	NS	NS
DR7	14.0	15.3	NS	NS
DRw8	5.3	2.9	NS	NS
DR9	0.0	0.7	NS	NS
DRw10	8.8	2.2	<0.01	NS
DR1 + DRw10	21.1	6.8	<0.0005	<0.02*
One antigen	31.6	54.4	<0.002	NS

* Relative risk = 3.7.
NS = not significant.

TABLE II Frequencies of HLA-B Antigens (%)

Antigen	Pts (n = 62)	Control Subjects (n = 1,416)
B5	0.0	1.3
B7	29.0	20.4
B8	9.7	12.9
B13	1.6	3.8
B14	1.6	5.7
B15	6.5	4.0
B16	4.8	3.3
B17	37.1	38.6
B18	3.2	5.2
B21	1.6	1.8
Bw22	1.6	0.07
B27	1.6	0.3
B35	11.3	6.7
B37	0.0	0.01
B40	0.0	0.6
Bw41	1.6	1.5
Bw42	21.0	23.5
B44	14.5	15.0
Bw47/47	0.0	0.1
Bw53	0.0	1.6
Bw70	25.8	14.2
One antigen	17.7	30.7

Difference not significant for all comparisons.

TABLE IV Frequencies of HLA-DQ Antigens (%)

Antigen	Pts (n = 57)	Control Subjects (n = 198)
DQw1	66.7	58.1
DQw2	14.0	23.4
DQw3	35.1	29.8
One antigen	84.2	88.9

Difference not significant for all comparisons.

selected diseases.⁸ Only 198 normal healthy black individuals had undergone DQ typing.

The HLA-A and HLA-B antigens were identified with a 2-stage lymphocytotoxicity test.⁹ These antigens were defined with 180 antisera, which consisted of local serum samples that had been requested for use in International Histocompatibility Workshops, local samples that had been verified by use in parallel with the International Workshop samples and samples that had been exchanged with other laboratories worldwide.¹⁰⁻¹⁴ Similarly, 120 serum samples were used to define the HLA-DR and HLA-DQ antigens in B cell-enriched lymphocyte suspensions prepared with the use of straws packed with nylon wool.¹⁵ The difference in frequency of the various antigens between patients and control subjects was tested for significance by means of the chi-square test (without Yates' correction). The resulting *p* values were multiplied by the number of HLA antigens tested to determine the corrected *p* value. Relative risk was calculated according to the method of Svejgaard et al.¹⁶

The percentage frequencies of the HLA-A, HLA-B, HLA-DR and HLA-DQ antigens in patients with idiopathic dilated cardiomyopathy and the control subjects are listed in Tables I to IV. With respect to the differences noted, only the increased frequency of the closely related antigens, HLA-DR1 and DRw10 (21.1 vs 6.8%), remained significant after correcting the *p* value (relative risk 3.7).

Associations between disease and the HLA system may involve class I (HLA-A, B or C) or class II antigens (D-locus antigens). In this study, no differences in frequency of any of the HLA-A, B or DQ antigens between black patients with idiopathic dilated cardiomyopathy and control subjects were detected. However, we found an increased frequency of the HLA-DR1 and DRw10 antigens in our patients with idiopathic dilated cardiomyopathy; the differences in frequencies between patients and control subjects remained significant after correcting for the total number of HLA antigens tested. The corrected *p* value would be <0.005 if a correction were made only for the number of DR antigens tested, as is done by some investigators.^{17,18}

Zerbe et al⁴ were unable to find an association between this disease and any of the class I and class II antigens in white patients. Another group observed an increased frequency of HLA-B27 and HLA-DR4 antigens and an underrepresentation of the HLA-DR6 in caucasoid patients with idiopathic dilated cardiomyopathy³; it is not stated whether the *p* values were corrected

for the number of antigens tested. An increased frequency of HLA-DR4 antigen was also noted in another group of caucasoid patients with this disease.⁵ Confirmation of a lack of an association between this disease and the HLA-DQ antigens will have to await further studies since these antigens were not tested in previous investigations.

Our study shows that idiopathic dilated cardiomyopathy in blacks is associated with certain DR antigens. This, together with the results of the study by Anderson et al³ and those of Limas and Limas,⁵ implies that genetically determined immune-response factors may play a role in the pathogenesis of this condition in some individuals.

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Positive Blood Cultures During Transesophageal Echocardiography

Günter Gorge, MD, Raimund Erbel, MD, Karl Jürgen Henrichs, MD, Hans-Martin Wenchel, MD, Heinz-Peter Werner, MD, and Jürgen Meyer, MD

Transesophageal echocardiography (TEE) is superior to transthoracic echocardiography in detecting thrombi, vegetations and abscess formation in patients with suspected endocarditis.¹ Because it is unclear, however, whether antibiotic prophylaxis is warranted during TEE, we investigated the rate at which bacteremia developed during TEE in 24 patients.

Starting January 1989 we took blood samples from patients undergoing TEE who had given informed consent. Initially we had anticipated a study size of 100 patients. We excluded patients with suspected endocarditis, other infective disease or artificial valves. Patient's skin at the site of venous puncture was disinfected using 80% ethanol and 2 venous blood samples were drawn. Additionally, we used cotton swabs to take smear samples from the throat and the surface of the gastroscope. We placed the swabs in sterile tubes (Suesse) together with growth media and processed them within 4 hours. Six to 12 minutes (mean $\pm$ standard deviation 9.96 ± 2.0) after the first attempt to introduce the echocardiographic probe, we drew 2 more venous blood samples at different and also thoroughly disinfected puncture sites. Blood culture bottles (Oxoid Inc.) had a temperature of 37°C before use and were processed immediately. During the examination, patients were in a left lateral decubitus position. We used a Toshiba SSH A 160 device and a gastroscope with a 3.5-MHz transducer attached to its tip (Olympus), 12 mm in diameter.

None of the blood samples obtained before TEE was positive. We stopped the study after 4 of 24 patients (17%) had positive blood cultures. Table I lists the bacteria isolated. None of the cultures taken from the echocardiographic probe was positive in these patients. Of the 4 patients with positive cultures, introduction of the echocardiographic probe was rather difficult in 2 (patients 1 and 2 in Table I), but without problems in patients 3 and 4. Two patients reported shivering shortly after the examination (patients 1 and 3), whereas all the others were free of symptoms indicative of transient bacteremia. During follow-up (4 to 6 months) no patient showed signs of endocarditis or any other bacteremia-induced illness.

The number of positive blood samples in a small number of consecutively studied patients was surprisingly high, especially in comparison with data obtained from patients undergoing upper gastrointestinal endoscopy. In their extensive reviews, Everett and Hirshman² and Bisno³ reported rates of positive blood cultures for

TABLE I Bacteria Identified from Throat Tissue Smears Before Transesophageal Echocardiography and Blood Samples Obtained During Transesophageal Echocardiography (3 and 4)

Pt	Throat	Blood	Sample No.
1	<i>Staphylococcus epidermidis</i>	<i>Staphylococcus epidermidis</i>	3
		<i>Staphylococcus epidermidis</i>	4
2	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	3
		<i>Staphylococcus epidermidis</i>	4
3	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> <i>Streptococcus viridans</i>	<i>Staphylococcus aureus</i>	3
		<i>Enterococcus durans</i>	4
		<i>Klebsiella oxytoca</i>	4
4	<i>Staphylococcus epidermidis</i> <i>Streptococcus viridans</i>	<i>Staphylococcus aureus</i>	3
		<i>Neisseria</i>	4

patients undergoing gastroduodenoscopies between 4 and 13%, with staphylococci the leading microorganism. Botoman and Surawicz⁴ reported positive blood cultures in 4.2% of their patients during gastroscopy; this increased to 45% in patients undergoing dilatation of the esophagus. The bacteria isolated were *Streptococcus viridans*, *Staphylococcus aureus* and *Staphylococcus epidermidis*. The rates of bacteremia thus seem to parallel the likelihood of trauma. The difference between these results and ours may be explained by the larger diameter of the gastroscope used for TEE and the possibly longer examination time in some patients. The spectrum of bacteria isolated was comparable, suggesting that the upper respiratory tract was the most likely site of invasion.

The sensitivity of blood cultures for showing bacteremia is relatively low, and there is no real "gold standard." We tried to keep false-negative results to a minimum by warming the blood samples before use and by processing them immediately. To prevent false-positive results, we thoroughly disinfected the skin and drew blood under sterile conditions. None of the cultures taken before the TEE was positive and this confirms that these precautions were effective. Laboratory contamination during processing is unlikely to occur only in the cultures prepared from blood obtained during TEE. Ideally, it would be necessary to take >2 blood samples before and 2 ten minutes after the first attempt to introduce the endoscope. On the other hand, we were aware of the discomfort our patients would have from >4 venous punctures. We decided to draw the blood samples after 10 minutes because we expected that the likelihood of bacteremia was highest in the early phase, because of micro injuries.

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We cannot rule out higher rates of positive blood cultures, however, if samples are drawn more often during TEE.

Although the number of patients in our study is too small to define the exact rate of bacteremia during TEE, bacteremia seems to be common. Because of the large number of patients who undergo TEE and have, for example, artificial valves or valve abnormalities and are thus at risk of acquiring bacterial endocarditis, we recommend that prophylactic steps be taken against endocarditis according to the guidelines of the American Heart Association⁵ for patient safety.

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CASE REPORT

Asymptomatic Persistent Fifth Aortic Arch (Congenital Double-Lumen Aortic Arch) in an Adult

Tal Geva, MD, Ronnie A. Ray, MD, Francesco Santini, MD, Stella Van Praagh, MD, and Richard Van Praagh, MD

Persistent fifth aortic arch in man is a rare anomaly, first described in 1969.¹ Since then, 15 additional cases have been reported, with severe associated congenital cardiac malformations in all.²⁻⁵ The purpose of this communication is to present the oldest documented case to date, a 31-year-old patient, with a previously unrecognized asymptomatic persistent fifth aortic arch. Another unique feature of this case is the absence of additional cardiovascular malformations apart from a secundum atrial septal defect.

A 31-year-old woman had progressive dyspnea on exertion and burning precordial chest pain relieved by antacids for 2 years. Her blood pressure was 105/80 mm Hg

with a regular heart rate of 96 beats/min. A prominent right precordial heave and a palpable pulmonary component were noted. The S₂ was widely split and had an increased pulmonary component. A pulmonary ejection click and a grade 1/6 diastolic murmur were noted along the left sternal border. Chest radiographs showed mild cardiac enlargement with both right atrial and right ventricular enlargement, prominent dilatation of the pulmonary artery and pruning of the intrapulmonary vasculature with peripheral oligemia. The electrocardiogram showed a frontal QRS axis of 144°, right atrial enlargement and right ventricular hypertrophy. Two-dimensional and Doppler echocardiograms showed bidirectional shunting across the atrial septum, right atrial and right ventricular enlargement and tricuspid regurgitation. Right-sided cardiac catheterization confirmed the bidirectional shunt at the atrial level with a 1.3 ratio of pulmonary to systemic

blood flow. The pulmonary arterial pressure decreased from 80/35 to 66/36 mm Hg after oxygen administration; the systemic pressure was 103/76 mm Hg.

On June 14, 1988, the patient underwent a primary closure of a secundum type of atrial septal defect. Cardiopulmonary bypass was used. The postoperative course was complicated by low cardiac output and pulmonary hypertension, which worsened despite inotropic support, vasodilators and an intraaortic balloon pump. The patient died on the second postoperative day.

Postmortem examination of the heart and lungs showed normal segmental combination, marked hypertrophy and enlargement of the right atrium and right ventricle, suture closure of the atrial septal defect and markedly dilated main pulmonary artery and branches with prominent atherosclerotic deposition. The aortic arch was left-sided with normal branching of the brachiocephalic vessels. A ligamentum arteriosum was present. The aortic arch was subdivided into superior and inferior channels (Figure 1). The superior channel gave rise to the brachiocephalic arteries and was considered to be composed distally of the left fourth aortic arch. The inferior channel originated proximally opposite the ostium of the innominate artery and rejoined the superior channel distally proximal to the ligamentum arteriosum. This inferior channel was considered to represent a persistent left fifth aortic arch (Figure 1A).

The 2 aortic arches were completely separated from each other by 2 separate adventitial layers, and a probe could be passed between them. The luminal diameter of the fourth aortic arch (8 mm) was slightly larger than the fifth aortic arch (6 mm), without obstruction of either aortic arch or coarctation of the aorta. The lungs were mildly congested. On microscopic examination, the pulmonary parenchyma showed mild congestion and a small focus of bronchopneumonia in the right upper lobe. Plexiform lesions were present in the pulmonary arterioles.

This case of persistent fifth aortic arch is different from the 15 previ-

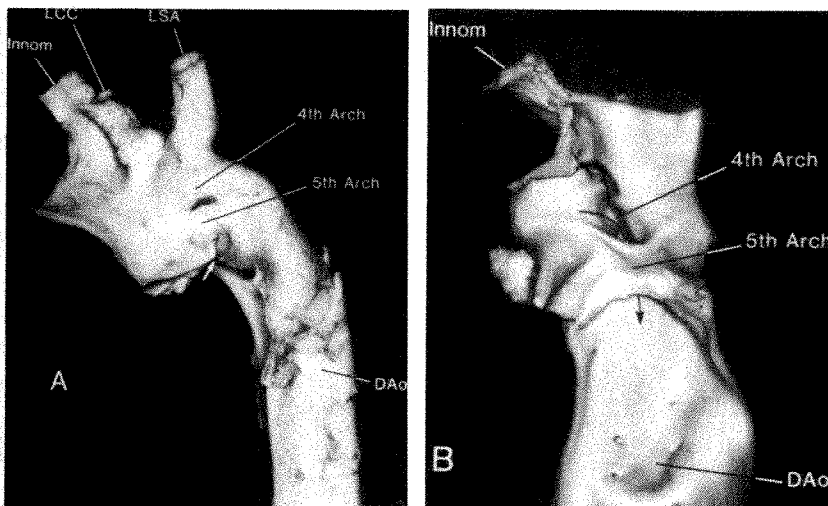


FIGURE 1. A, external anterior view of the aortic arches. The left fourth arch (4th arch) gives rise to the brachiocephalic arteries in a normal fashion. The fifth left arch (5th arch) begins opposite the innominate artery (Innom), runs below and rejoins the fourth arch proximal to ligamentum arteriosum (arrow). Note the 2 separate adventitial layers of each aortic arch. B, internal view of the aortic arches. There is a double lumen with the fourth arch being the superior channel (arrow), and the fifth arch being the inferior channel. DAo = descending aorta; LCC = left common carotid artery; LSA = left subclavian artery.

ously reported cases in 2 respects. First, it is the oldest documented case. In their analysis of published reports, Herrera,² Gerlis³ and their co-workers showed that 8 of 11 patients in whom the age was known died during the first year of life from associated cardiac malformations. The mean age at death of all previously published cases was 22 months (range birth to 8.5 years).

Second, except for a secundum type of atrial septal defect, this patient had no other significant cardiac malformation. The persistent fifth aortic arch in our patient was hemodynamically insignificant and was found unexpectedly at autopsy. All previously reported cases had severe associated cardiac malformations including pulmonary atresia (8 of 15), ventricular septal defect (7 of 15), tricuspid atresia (4 of 15), coarctation of aorta (4 of 15), patent ductus arteriosus (4 of 15), cor triatriatum (2 of 15), transposition of the great arteries (2 of 15), interrupted aortic arch (1 of 15), single right coronary artery (1 of 15), aortopulmonary

window (1 of 15), pulmonary stenosis (1 of 15) and interrupted right pulmonary artery (1 of 15).

In 9 of 15 cases (60%), persistent fifth aortic arch was associated with markedly reduced pulmonary blood flow secondary to severe right-sided outflow tract stenosis or atresia. The coexistence of right ventricular outflow tract obstruction and persistence of the fifth aortic arch may be developmentally significant. At the time of the establishment of the sixth (pulmonary) arch in man, Congdon⁶ found that 50% of human embryos have a fifth arch. These observations suggest the hypothesis that patients with a congenital double-lumen aortic arch represent an arrest at the fifth aortic arch stage, when the pulmonary arterial system is early in its development, as in Congdon's embryo no. 617 (7 mm in length, estimated gestational age 28 to 30 days, Carnegie stage XIV).⁶

From the diagnostic standpoint, it is important to be familiar with this congenital malformation so that one can differentiate it from aortic dis-

section based on the typical appearance of the double lumen. The lower channel (fifth arch) runs below the upper channel (fourth arch) like a "subway" between the origin of the innominate artery proximally and the origin of the left subclavian artery distally. This typical appearance can be detected by 2-dimensional echocardiography, angiography or magnetic resonance imaging.

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Making Clinical Studies Involving Many Patients Useful to the Single Patient

"Doctoring" centers on the single patient, the 1-to-1 relationship. Yet most clinical studies published in medical journals involve many patients. How can articles in medical journals be presented such that practitioners can fit their single patient into a large clinical study? Two suggestions:

1. Keep patient populations as homogenous as possible: I was surprised when becoming a medical journal editor 8 years ago how heterogeneous were some patient populations included in various studies. An example: a manuscript on the effects of 1 or more drugs on ventricular tachycardia typically might include 80 patients in whom the ventricular tachycardia was associated with atherosclerotic coronary artery disease, 25 patients in whom it was associated with idiopathic dilated cardiomyopathy, 5 patients with mitral valve prolapse, 4 patients who earlier had had valve replacement for aortic valve disease, 3 patients with "hypertensive heart disease," 5 patients who earlier had had tetralogy of Fallot repaired, and 10 patients without structural heart disease. The results of the study were pooled together so that it was impossible to know whether or not the results were similar in the various conditions associated with the ventricular tachycardia. In these circumstances I have asked authors to limit their study to the 80 patients with ventricular tachycardia associated with coronary artery disease, often with the comment that when the numbers of patients with the other conditions were large enough that another manuscript focusing on that group would be welcomed.

Another example: another area where a heterogeneous population is likely to be found are studies describing the effects of 1 or more drugs in patients with congestive heart failure. A study might include 20 patients in whom the chronic congestive heart failure was associated with coronary artery disease (ischemic cardiomyopathy), 10 patients with idiopathic dilated cardiomyopathy, 3 patients with pure mitral regurgitation, 2 patients who earlier had had aortic valve replacement for reasons unspecified, 4 patients with "hypertensive heart disease" and 2 patients in whom the etiology of the heart failure was not determined. In this circumstance I ask the authors to limit their study to the patients with congestive heart failure associated with coronary artery disease and with idiopathic dilated cardiomyopathy and to separate the data by these 2 etiologic groups.

Another "trap" may occur in manuscripts reporting results of valve replacement of 1 or more cardiac valves or results using a particular type of mechanical prosthesis or bioprostheses. In these circumstances, it is important of course not to intermix results of replacement of 1 cardiac valve (e.g., mitral) with that of another cardiac valve (e.g., aortic). Additionally, it is useful to be able to determine results when valve replacement was performed for pure valvular regurgitation as opposed to that performed

for valve stenosis (with or without associated regurgitation) because the etiologies of the stenotic lesions are usually entirely different from those of the purely regurgitant lesions.¹

2. Provide individual patient data rather than pooled data: Many manuscripts submitted to medical journals report on 10 or so patients, and, surprisingly, despite the small numbers, the data are pooled. In studies involving up to 30 patients it is preferable to present the pertinent data in each patient. To present individual patient data in studies involving 30 patients, however, much care must be exerted in formulating a table. With rare exception, no patient should occupy more than 1 line across. Each column must ask a precise question that is answerable by either a number or by a "+" (positive or present), a "0" (negative or absent) or by a "-" (no information available). Writing within the body of a table usually indicates that a precise question has not been formulated and that the table needs additional work. In my own manuscripts I spend far more time on the tables and figures than I do on the writing of the text.

Another important aspect of tables presenting individual patient data is that in this way data points ("holes") that are missing are readily discernible. When data are pooled, missing data points usually cannot be detected. I have been surprised on occasion when returning a manuscript to an author requesting an individual patient table rather than a pooled data table to find many pertinent data items in some patients to be unavailable. Thus, presenting individual patient data tables allows the reader to insert his/her single patient more readily into a study, and it also provides a good means for detecting missing data. Of course, individual patient variability is more readily detected by presentation of individual patient data.

Thus, study populations should be as homogenous as possible, and tables displaying individual patient data are preferable to those showing pooled data.



William C. Roberts

William Clifford Roberts, MD
Editor in Chief

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Physician Inertia in Dealing with Hypercholesterolemia Discovered During Hospitalization

Kudos to William Roberts, Editor in Chief of *The American Journal of Cardiology*, for this article entitled "Lipid-Lowering Therapy After an Atherosclerotic Event."¹ With a clarity that belies the careful consideration given to a difficult and controversial subject, Dr. Roberts has made the case for lipid-lowering therapy after an atherosclerotic event. He clearly states that we must treat serum cholesterol levels in persons after an acute atherosclerotic event differently from the so-called standard population at risk.

While there will be opponents to his viewpoint, particularly since many physicians have become resentful of the media hype related to the National Cholesterol Education Program, the validity of this approach has been established by the many references cited.

In this controversial and confrontational area of therapy, little has been said about the physician inertia that preceded the current therapeutic enthusiasm for both drugs and diet. In 1986, I reported on "Hypercholesterolemia During Hospitalization."² In that article, I identified 38 patients admitted to a medical school teaching hospital in upstate New York in whom a cholesterol level >350 mg/dl was noted during hospital admission. Patients with clearly identified secondary hyperlipidemia such as due to thyroid disease, nephrotic syndrome, lymphoma, biliary cirrhosis and diabetic ketoacidosis were excluded. The cholesterol in this group of patients varied from 351 to 1,060 mg/dl; yet during the hospitalization only 14 of them had cholesterol measurements repeated, and only in 13 was the diagnosis of hyperlipidemia made. The physician wrote a dietary order related to hyperlipidemia in only 9 cases. Twenty-three of these patients had documented vascular disease during their present hospital stay including coronary artery disease, peripheral vascular disease and cerebral vascular disease.

One patient, a 40-year-old male smoker with a history of coronary artery disease and hypertension, had a cholesterol level of 474 mg/dl, and received neither dietary nor drug therapy. The diagnosis of hyperlipidemia had not been noted on this patient's chart and no lipid determinations were made during follow-up.

While the cost of lipid-lowering dietary and drug therapy is real, and there is room for further research into the effect of such therapy in women and the elderly, the necessity for treatment has been clearly outlined.

For those therapeutic nihilists who take objection to the current media blitz on cholesterol, perhaps a closer analysis of the situation in American teaching hospitals before the National Cholesterol Education Program merits attention.

David T. Nash, MD
Syracuse, New York
2 October 1989

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Maternal and Fetal Sequelae of Anticoagulation During Pregnancy

In the study by Sareli et al,¹ the finding of a high incidence of fetal wastage was not surprising, since warfarin is a known teratogen.¹⁻⁴ Heparin has been shown to be relatively safe and effective during pregnancy in the setting of prosthetic valves.^{5,6} Because of warfarin's known teratogenicity, and the existence of a safe alternative therapy, it seems logical that heparin should be used instead of warfarin in this clinical setting.

The study by Sareli et al raises certain issues of concern. Physicians would be placing themselves at great risk of liability for prescribing warfarin to a pregnant woman or a woman thinking of having children. Any woman of childbearing age should be advised to stop taking warfarin before becoming pregnant. Subcutaneous heparin can be safely substituted before conception, whether for prosthetic valves or deep vein thrombosis prophylaxis.⁶

We believe the issue of warfarin teratogenicity is well enough established to obviate the need for future studies placing unborn children at risk for fetal malformations, hemorrhage or death.

Keith E. Myers, MD
Jeffrey M. Nakamura, MD
Honolulu, Hawaii
23 August 1989

1. Sareli P, England MJ, Berk MR, Marcus RH, Epstein M, Driscoll J, Meyer T, McIntyre J, van Gelderen C. Maternal and fetal sequelae of anticoagulation during pregnancy in patients with mechanical heart valve prosthesis. *Am J Cardiol* 1989;63:1462-1465.

2. Avery GS, ed. Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics, second edition. New York: ADIS Press, 1980:467.
3. Shaul WL, Hall JG. Multiple congenital abnormalities associated with oral anticoagulants. *Am J Ob Gyn* 1977;127:191.
4. Physicians' Desk Reference, 1989.
5. Lee PK, Wang RYC, Chow JSF, et al. Combined use of warfarin and adjusted subcutaneous heparin during pregnancy in patients with artificial heart valves. *JACC* 1986;8:221-224.
6. Salazar E, Zajarias A, Gutierrez N, Iturbe I. The problem of cardiac valve prosthesis, anticoagulants, and pregnancy. *Circulation* 1984; 70(suppl 1):1-169-1-177.

REPLY: We fully agree with these comments regarding the substitution of warfarin by heparin before conception to avoid warfarin embryopathy in live-born infants in patients with prosthetic valves. Unfortunately, as we stated in our article no "patients had reported for preconceptual counseling," probably based on some cultural tradition. They continued to take warfarin throughout the first trimester. However the documented rate of embryopathy in live-born infants in our study group was only 4%, which is relatively low. We stated at the end of our article that "controlled studies of heparin anticoagulation started before conception and continued throughout pregnancy may improve fetal prognosis in this group of patients."

Pinhas Sareli, MD
Johannesburg, South Africa
26 September 1989

Correction

In the July 18, 1989, *AJC* symposium issue, Table I on page 30B is incorrect. The columns under the Coumarin Therapy and Placebo Group headings should be switched. The corrected Table appears here:

TABLE I Main Findings of the Dutch Sixty Plus Reinfarction Study³

	Coumarin Therapy (n = 439)	Placebo Group (n = 439)	p Value
Reinfarction			
Receiving treatment	20	58	0.0001
Intention to treat	29	64	0.0005
Deaths			
Receiving treatment	28	49	0.017
Intention to treat	51	69	0.071

The American Journal of Cardiology

JUNE 15, 1990

19-4-91



VCM
1411 **Coronary Artery Disease**

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Conduction Disturbances**

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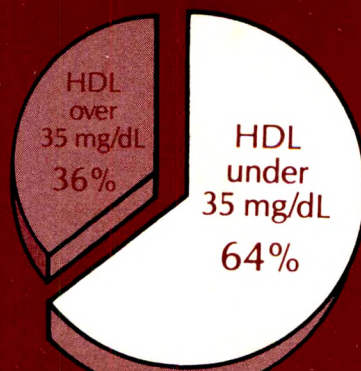
240 TOTAL

<35 HDL
mg/dL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,¹ and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.²

HEART ATTACK PATIENTS
(PROCAM TRIAL)²



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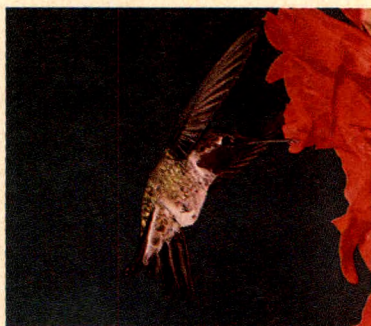
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And see the pacemaker that travels light... and responds instantly. Sensolog III.

CORONARY ARTERY DISEASE**1411****The Prehospital Phase of Acute Myocardial Infarction in the Era of Thrombolysis**

Stanley B. Schmidt and Mark A. Borsch

A detailed questionnaire was given to 126 patients with acute myocardial infarction to evaluate factors affecting the time between symptom onset and hospital arrival; the mean prehospital time was 5.9 ± 11.0 hours. Stepwise multiple regression identified slow symptom progression, low income, female gender and advanced age as independent predictors of prehospital time ($p < 0.03$); logistic regression also selected slow symptom progression, female gender and low income as significant ($p \leq 0.02$) independent predictors. Data indicate it is possible to profile patients likely to experience undue prehospital delay during AMI, which may be of importance to future educational efforts.

1416**Prediction of Preserved Flow to the Infarct Area Based on Admission Electrocardiogram in Anterior Wall Acute Myocardial Infarction**

Yasuhiko Tanabe, Akio Matsuoka, Masaaki Okabe, Hideaki Otsuka, Masashi Takahashi, Hidenori Kato, Shigetaka Kasuya, Isao Sakashita, Masaru Yamazoe, Yusuke Tamura, Taku Matsubara, Yutaka Igarashi, Senji Hayashi, and Akira Shibata

To determine whether preserved flow to the infarct area and chronic phase regional wall motion after reperfusion could be predicted from the admission electrocardiogram, we studied 20 anterior myocardial infarction patients. Admission electrocardiographic findings of $\Sigma R/\Sigma ST > 2.5$ or $\Sigma ST < 2.0$ mV indicated preserved flow to the infarct area and relatively good regional wall motion in the convalescent stage after successful reperfusion.

1422**Reocclusion Three Months After Successful Thrombolytic Treatment of Acute Myocardial Infarction with Anisoylated Plasminogen Streptokinase Activating Complex**

Bert H. Takens, Johan Brügemann, Jan van der Meer, Peter den Heijer, and Kong I. Lie

We evaluated 30 patients with acute myocardial infarction treated with anisoylated plasminogen streptokinase activating complex. Oral anticoagulants may be less effective in the prevention of reocclusion; late reocclusion appeared to be less deleterious than initial thrombolytic failure.

1425**Influence of Heparin Therapy on Percutaneous Transluminal Coronary Angioplasty Outcome in Unstable Angina Pectoris**

Mary Ann Lukas Laskey, Ezra Deutsch, Elliot Barnathan, and Warren K. Laskey

The immediate procedural success of percutaneous transluminal coronary angioplasty in 135 patients with unstable angina receiving ≥ 24 hours of preprocedural intravenous heparin was significantly increased (91%) when compared to a similar group of 169 patients not receiving such therapy (81%, $p = 0.02$). Procedural failure due to abrupt thrombotic occlusion of the dilated vessel was more frequent in the nonheparin group (8.3%) than in the heparin-treated group (1.5%, $p < 0.01$). Data indicate that prolonged intravenous heparin therapy before PTCA in patients with unstable angina contributes to an improved success rate and a lower risk of thrombotic vessel occlusion.

1430**Transluminal Atherectomy of Saphenous Vein Aortocoronary Bypass Grafts**

Urs P. Kaufmann, Kirk N. Garratt, Ronald E. Vlietstra, and David R. Holmes, Jr.

Percutaneous transluminal atherectomy was performed in 14 patients with stenotic lesions in aortocoronary bypass grafts using the Simpson-designed directional coronary atherectomy catheter; atherectomy was successful in 13 (93%) of 14 patients and the mean stenosis was decreased from 85 to 15%. Percutaneous atherectomy may be performed in saphenous vein grafts with a higher degree of safety and efficacy than that usually associated with balloon angioplasty of vein graft lesions. However, preliminary follow-up angiographic data indicate that restenosis may occur in vein grafts after atherectomy at about the same rate as it occurs after balloon angioplasty.

1434**Long-Acting, Marked Antiischemic Effect Maintained Unattenuated During Long-Term Interval Treatment with Once-Daily Isosorbide-5-Mononitrate in Sustained-Release Form**

Andrea Beyerle, Günther Reiniger, and Werner Rudolph

Using a placebo-controlled protocol, we investigated the extent and duration of antiischemic effects of 50 and 100 mg isosorbide-5-mononitrate in sustained-release form in 18 patients with documented coronary artery disease. There is no evidence for tolerance development; we documented a marked fluctuation of IS-5-MN plasma concentration within the 24-hour treatment cycle, prerequisite to a successful interval treatment.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1438

Effects of Isoproterenol on Accessory Pathway Conduction in Intermittent or Concealed Wolff-Parkinson-White Syndrome

Toshio Yamamoto, San-Jou Yeh, Fun-Chung Lin, and Delon Wu

The effects of isoproterenol were evaluated in 24 patients with intermittent and 60 patients with concealed ventricular pre-excitation. Isoproterenol enhances anterograde accessory pathway conduction in patients with intermittent preexcitation with shortening of the longest atrial paced cycle length that induces block in the accessory pathway and the anterograde effective refractory period. It has no effect on anterograde conduction of the concealed accessory pathway. Isoproterenol enhances retrograde accessory pathway conduction by shortening the longest ventricular paced cycle length that induces retrograde block in the accessory pathway and the retrograde effective refractory period.

VALVULAR HEART DISEASE

1443

Validation and Applications of Mitral Prosthetic Valvular Areas Calculated by Doppler Echocardiography

Jean G. Dumesnil, George N. Honos, Michel Lemieux, and Jocelyn Beauchemin

The validity and relative usefulness of Doppler echocardiographic mitral valve gradient and area measurements were examined in a group of 26 patients 19 $\pm$ 4 months after implantation of different sizes of a given type of bioprosthesis. Areas obtained by the continuity equation method correlated well with known in vitro bioprosthetic areas ($r = 0.82$), whereas half-time areas correlated poorly ($r = 0.15$), and overestimated the in vitro area range in 69% of cases. The projected relations between indexed prosthetic areas and pressure gradients may be helpful in prosthesis selection to avoid patient-prosthesis mismatch.

CARDIOMYOPATHY

1449

Clinical and Pathologic Study of Familial Dilated Cardiomyopathy

Luisa Mestroni, Daniela Miani, Andrea Di Lenarda, Furio Silvestri, Rossana Bussani, Giorgio Filippi, and Fulvio Camerini

To evaluate the occurrence of familial dilated cardiomyopathy, we studied 165 consecutive patients, and identified 43 patients with confirmed or suspected myocardial disease in the families of the 12 patients showing evidence of myocardial disease in ≥ 1 relative. The various forms of genetic transmission and manifestations of myocardial diseases in the same family suggest that familial DC is a multifactorial syndrome.

MISCELLANEOUS

1454

Influence of Aging on Pulmonary Hemodynamics in a Population Free of Coronary Artery Disease

William R. Davidson and Eric C. Fee

To determine the influence of aging on pulmonary hemodynamics in subjects without angiographically demonstrable coronary disease or left ventricular systolic dysfunction (ejection fraction $\geq 50\%$ and left ventricular end-diastolic pressure < 14 mm Hg), 47 normal subjects were identified out of 5,508 consecutive cardiac catheterizations. In group I (age ≥ 60 years), mean pulmonary artery pressure (16 ± 3 mm Hg), vascular resistance (124 ± 32 dynes s cm^{-5}) and pulmonary/systemic resistance ratio (0.099 ± 0.046) were higher than in group II (age < 60 years) at 12 ± 2 mm Hg, 70 ± 25 dynes s cm^{-5} and 0.057 ± 0.019 , respectively (all p values < 0.01 to 0.001). All pulmonary hemodynamic variables increased with age, a change not attributable to coronary disease or left ventricular systolic dysfunction.

1459

Prognostic Value of Intravenous Dipyridamole Thallium Imaging in Patients with Diabetes Mellitus Considered for Renal Transplantation

Alan D. Camp, Paul J. Garvin, Judy Hoff, Jeanne Marsh, Sheila L. Byers, and Bernard R. Chaitman

To determine the effectiveness of intravenous dipyridamole thallium imaging in predicting cardiac events, 40 diabetic renal transplant candidates were studied preoperatively in a prospective trial. The study group consisted of 40 patients whose average age was 42 years (range 27 to 64); 34 (85%) were hypertensive and 21 (53%) were cigarette smokers. Data indicate that dipyridamole imaging is an effective method of identifying renal transplant candidates likely to develop cardiac complications.

1464

Superior Vena Cava Doppler Flow Velocity Patterns in Pericardial Disease

Benjamin F. Byrd, III, and Ryk W. Linden

Doppler superior vena cava flow patterns were studied in 34 patients with pericardial disease and in 8 normal adults; characteristic flow variations during respiratory monitoring were identified in cardiac tamponade and constrictive pericarditis. Our data indicate that quantitative analysis of SVC flow velocity patterns is a useful addition to the echocardiographic evaluation of pericardial disease.

1471

Transient Alterations in Cardiac Performance After a Six-Hour Race

Ignasi Carrió, Ricard Serra-Grima, Lluís Berná, Montserrat Estorch, Carlos Martinez-Duncker, and Jordi Ordoñez

We performed technetium-99m-albumin gated blood pool scans and injected indium-111 antimyosin in 10 long distance runners immediately after a 6-hour competitive race. We then obtained antimyosin scans and performed gated blood pool scans 48 hours later. Antimyosin scans were normal in 7 athletes and 3 experienced minimal antimyosin myocardial uptake.

1475

The Electrocardiogram at Rest and Exercise During a Simulated Ascent of Mt. Everest (Operation Everest II)

Mark Malconian, Paul Rock, Herbert Hultgren, Howard Donner, Alan Cymerman, Bertron Groves, John Reeves, James Alexander, John Sutton, Masao Nitta, and Charles Houston

Eight healthy young men participated in this study of the effects of extreme altitude on cardiac function. Electrocardiograms were recorded at rest and during maximal exercise at several simulated altitudes up to 8,840 m. Our results show that extreme altitude exposure causes electrocardiographic changes compatible with pulmonary hypertension and that maximal exercise at 8,840 is not accompanied by any electrocardiographic evidence of ischemia despite severe hypoxemia and alkalosis.

1481

Thrombotic and Cardiovascular Complications Related to Nonionic Contrast Media During Cardiac Catheterization: Analysis of 8,517 Patients

Charles J. Davidson, Daniel B. Mark, Karen S. Pieper, Katherine B. Kisslo, Mark A. Hlatky, Don A. Gabriel, and Thomas M. Bashore

Thrombotic and cardiovascular complications were prospectively evaluated in 8,517 consecutive patients undergoing diagnostic cardiac catheterization with nonionic contrast media. Thrombotic events occurred in 15 patients (0.18%), 7 of whom had a coronary artery thrombus or embolus. Although thrombotic events have unusual temporal clustering and result in major complications, the overall incidence is low and comparable to previous studies using ionic contrast agents.

METHODS

1485

Comparison with Radionuclide Angiography of Two New Geometric and Four Nongeometric Models for Echocardiographic Estimation of Left Ventricular Ejection Fraction Using Segmental Wall Motion Scoring

Robert D. Rifkin and Hitoshi Koito

We used 2-dimensional echocardiography to visually score wall motion in 12 regions of the left ventricle. From these scores, we then compared 2 new methods of determining ejection fraction with radionuclide angiography in 50 patients. Results show that wall motion scores can be translated into accurate estimates of ejection fraction by geometric models and by simple linear combinations of wall motion scores when the latter are based on appropriate geometric assumptions with proper weight given to each segment.

1491

Measurement of Intracardiac Dimensions and Structures in Normal Young Adult Subjects by Transesophageal Echocardiography

Michael Drexler, Raimund Erbel, Udo Müller, Norbert Wittlich, Susanne Mohr-Kahaly, and Jürgen Meyer

Standardized measurements of well-defined transesophageal cross-sectional planes were performed in 25 healthy volunteers. The left ventricular short-axis view and the 2- or 4-chamber view with the left and right atrium, the long-axis view of the left and right ventricle, the mitral and tricuspid valve ring and the atrial septum were analyzed in end-diastole and end-systole; the aortic valve plane, the diameters of the ascending and descending aorta and the pulmonary artery stem were also measured. The normal values obtained in healthy young subjects should be taken into account in diagnostic decision making in heart patients.

EDITORIAL

1497

Pharmacologic Management of Ventricular Arrhythmias After the Cardiac Arrhythmia Suppression Trial

Joel Morganroth and J. Thomas Bigger, Jr.

1504

Effects of Left Ventricular Hypertrophy on the Coronary Circulation

Kevin C. Dellsperger and Melvin L. Marcus

BRIEF REPORTS

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Association of Mitral Annular Calcium with New Thromboembolic Stroke and Cardiac Events at 39-Month Follow-Up in Elderly Patients

Wilbert S. Aronow, Mordecai Koenigsberg, Itzhak Kronzon, and Hal Gutstein

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Fractal Clustering of Ventricular Ectopy in Dilated Cardiomyopathy

Kenneth M. Stein and Paul Kligfield

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CASE REPORT

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Distension of the Oblique Pericardial Sinus in Tamponade due to Loculated Posterior Pericardial Effusion

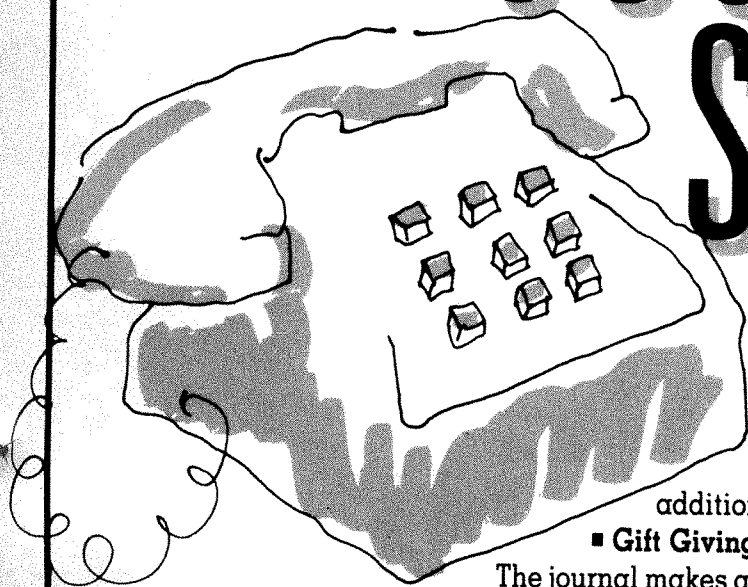
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Stanley B. Schmidt and Mark A. Borsch

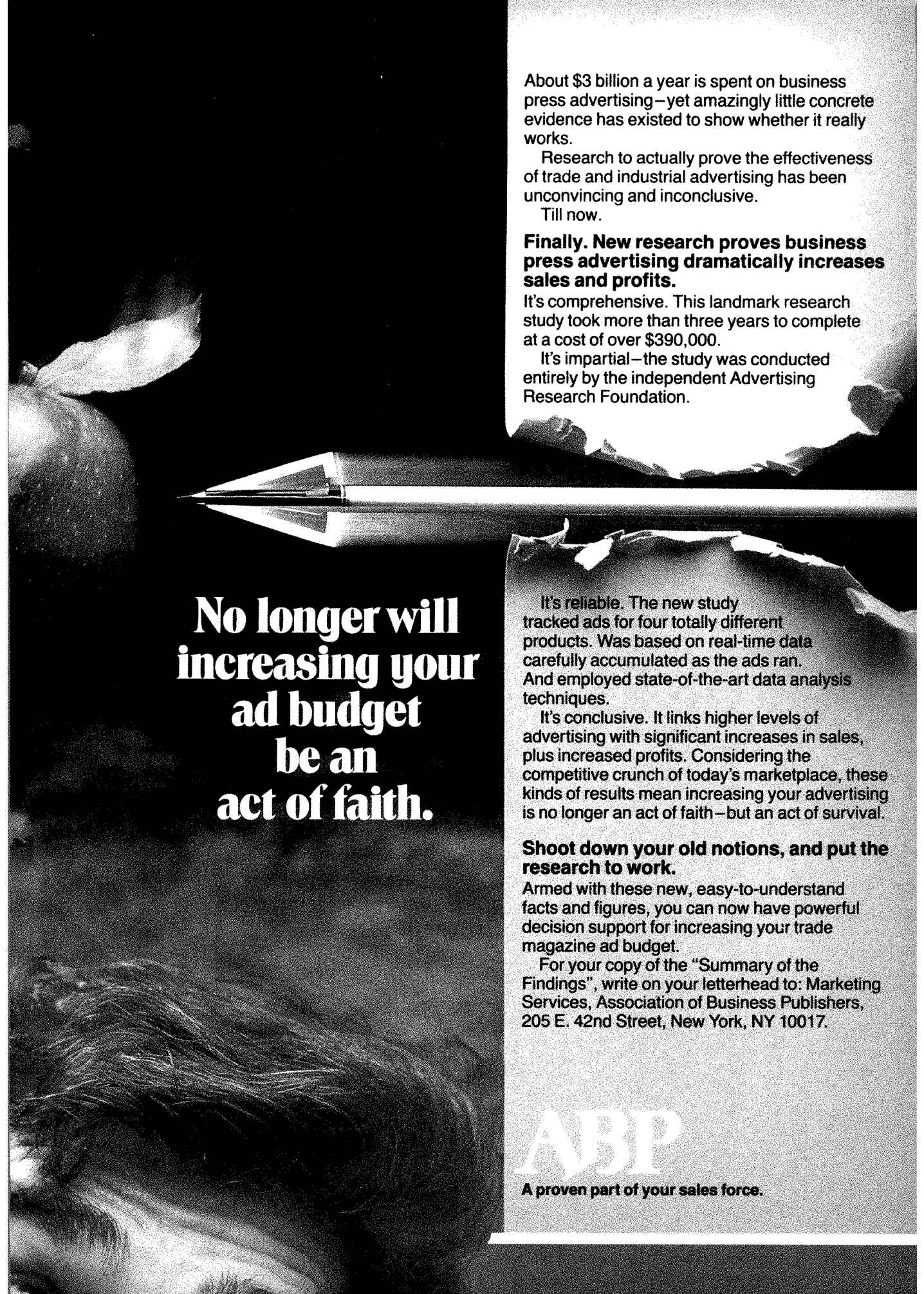
A detailed questionnaire was given to 126 patients with acute myocardial infarction (AMI) to evaluate factors affecting the time between symptom onset and hospital arrival. The mean prehospital time was 5.9 ± 11.0 hours. The time between symptom onset and reaching a decision that medical care should be sought was 62% of mean prehospital time. Stepwise multiple regression identified the following 4 variables as independent predictors of prehospital time: slow symptom progression; low income; female gender; and advanced age. All of these variables were predictive ($p < 0.03$) of increased prehospital time. Similarly, logistic regression analysis selected slow symptom progression, female gender and low income as significant ($p \leq 0.02$) independent predictors of prehospital time > 6 hours. These data indicate it is possible to profile patients likely to experience undue prehospital delay during AMI, which may be of importance to future educational efforts.

1416**Prediction of Preserved Flow to the Infarct Area Based on Admission Electrocardiogram in Anterior Wall Acute Myocardial Infarction**

Yasuhiko Tanabe, Akio Matsuoka, Masaaki Okabe, Hideaki Otsuka, Masashi Takahashi, Hidenori Kato, Shigetaka Kasuya, Isao Sakashita, Masaru Yamazoe, Yusuke Tamura, Taku Matsubara, Yutaka Igarashi, Senji Hayashi, and Akira Shibata

To determine whether preserved flow to the infarct area and chronic phase regional wall motion after reperfusion could be predicted from the admission electrocardiogram, we studied 20 anterior myocardial infarction patients. Patients with preserved flow to the infarct area showed significantly lower ΣST and significantly higher $\Sigma R/\Sigma ST$ than patients without preserved flow. Chronic phase regional wall motion was correlated with $\Sigma R/\Sigma ST$ ($r = 0.75$) or ΣST ($r = -0.65$). All except 1 patient with preserved flow showed $\Sigma R/\Sigma ST > 2.5$ or $\Sigma ST < 2.0$ mV. Thus, admission electrocardiographic findings of $\Sigma R/\Sigma ST > 2.5$ or $\Sigma ST < 2.0$ mV indicated preserved flow to the infarct area and relatively good regional wall motion in the convalescent stage after successful reperfusion.

Continued on page A18



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1422**Reocclusion Three Months After Successful Thrombolytic Treatment of Acute Myocardial Infarction with Anisoylated Plasminogen Streptokinase Activating Complex**

Bert H. Takens, Johan Brügemann, Jan van der Meer, Peter den Heijer, and Kong I. Lie

We evaluated 30 patients with acute myocardial infarction treated with anisoylated plasminogen streptokinase activating complex. Angiography was performed at 1.5 and 48 hours. Reocclusion was determined after 3 months. Patency at 1.5 and 48 hours amounted to 65 and 69%, respectively. No reocclusion within 48 hours was found. The mean residual diameter stenosis of the patent infarct-related vessels decreased from 56 to 46% between 1.5 and 48 hours ($p < 0.01$). Patients with an occluded vessel at 1.5 hours demonstrated quick deterioration of the ejection fraction. Clinically silent reocclusion at 3 months, without an associated decrease of the ejection fraction, was found in 28% of the patients despite oral anticoagulation. Oral anticoagulants may be less effective in the prevention of reocclusion. Late reocclusion appeared to be less deleterious than initial thrombolytic failure.

1425**Influence of Heparin Therapy on Percutaneous Transluminal Coronary Angioplasty Outcome in Unstable Angina Pectoris**

Mary Ann Lukas Laskey, Ezra Deutsch, Elliot Barnathan, and Warren K. Laskey

The immediate procedural success of percutaneous transluminal coronary angioplasty (PTCA) in 135 patients with unstable angina receiving ≥ 24 hours of preprocedural intravenous heparin was significantly increased (91%) when compared to a similar group of 169 patients not receiving such therapy (81%, $p = 0.02$). Procedural failure due to abrupt thrombotic occlusion of the dilated vessel was more frequent in the nonheparin group (8.3%) than in the heparin-treated group (1.5%, $p < 0.01$). Our data indicate that prolonged intravenous heparin therapy before PTCA in patients with unstable angina contributes to an improved success rate and a lower risk of thrombotic vessel occlusion.

1430**Transluminal Atherectomy of Saphenous Vein Aortocoronary Bypass Grafts**

Urs P. Kaufmann, Kirk N. Garratt, Ronald E. Vlietstra, and David R. Holmes, Jr.

Percutaneous transluminal atherectomy was performed in 14 patients with stenotic lesions in aortocoronary bypass grafts using the Simpson-design directional coronary atherectomy catheter. Atherectomy was successful in 13 (93%) of 14 patients; the mean stenosis was reduced from 85 to 15%. Unsuccessful atherectomy was associated with vascular collapse and death, precipitated by acute native vessel closure after balloon angioplasty in 1 patient. Minor complications occurred in 3 patients. Percutaneous atherectomy may be performed in saphenous vein grafts with a higher degree of safety and efficacy than that usually associated with balloon

Continued on page A25

angioplasty of vein graft lesions. However, preliminary follow-up angiographic data indicate that restenosis may occur in vein grafts after atherectomy at about the same rate as it occurs after balloon angioplasty.

1434

Long-Acting, Marked Antiischemic Effect Maintained Unattenuated During Long-Term Interval Treatment with Once-Daily Isosorbide-5-Mononitrate in Sustained-Release Form

Andrea Beyerle, Günther Reiniger, and Werner Rudolph

In 18 patients with documented coronary artery disease, the extent and duration of antiischemic effects of 50 and 100 mg isosorbide-5-mononitrate (IS-5-MN) in sustained-release form were investigated using a placebo-controlled protocol. After the initial administration of both dosages, there were significant reductions in exercise-induced ST-segment depression and increases in ischemia-free exercise time up to 12 hours. After 3 weeks of long-term treatment, compared to the acute effect, the antiischemic action was documented to be equivalent. Accordingly, there is no evidence for tolerance development. A marked fluctuation of IS-5-MN plasma concentration within the 24-hour treatment cycle was documented, prerequisite to a successful interval treatment.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1438

Effects of Isoproterenol on Accessory Pathway Conduction in Intermittent or Concealed Wolff-Parkinson-White Syndrome

Toshio Yamamoto, San-Jou Yeh, Fun-Chung Lin, and Delon Wu

The effects of isoproterenol were evaluated in 24 patients with intermittent and 60 patients with concealed ventricular preexcitation. Isoproterenol enhances anterograde accessory pathway conduction in patients with intermittent preexcitation with shortening of the longest atrial paced cycle length that induces block in the accessory pathway and the anterograde effective refractory period. It has no effect on anterograde conduction of the concealed accessory pathway. Isoproterenol enhances retrograde accessory pathway conduction by shortening the longest ventricular paced cycle length that induces retrograde block in the accessory pathway and the retrograde effective refractory period.

VALVULAR HEART DISEASE

1443

Validation and Applications of Mitral Prosthetic Valvular Areas Calculated by Doppler Echocardiography

Jean G. Dumesnil, George N. Honos, Michel Lemieux, and Jocelyn Beauchemin

The validity and relative usefulness of Doppler echocardiographic mitral valve gradient and area measurements were examined in a group of 26 patients 19 ± 4 months after implantation of different sizes (25 to 31) of a given type of bioprosthesis. Areas obtained by the continuity equation method correlated well with known in vitro bioprosthetic areas ($r = 0.82$, standard error of the estimate = 0.1 cm^2 , $p < 0.001$), whereas half-time areas correlated poorly ($r = 0.15$, $p > 0.3$), and overestimated the in vitro area range in 69% of cases. The projected relations between indexed prosthetic areas and pressure gradients may be helpful in prosthesis selection to avoid patient-prosthesis mismatch.

CARDIOMYOPATHY

1449

Clinical and Pathologic Study of Familial Dilated Cardiomyopathy

Luisa Mestroni, Daniela Miani, Andrea Di Lenarda, Furio Silvestri, Rossana Bussani, Giorgio Filippi, and Fulvio Camerini

To evaluate the occurrence of familial dilated cardiomyopathy (DC), 165 consecutive patients were studied. Twelve patients (7%) showed evidence of myocardial disease in ≥ 1 relative; 43 patients with confirmed or suspected myocardial disease were identified in the 12 families. In 6 families, proband and relatives were affected by DC (total 14 cases); in 1 of these families the disease began with atrioventricular block. In 4 families, relatives showed myocarditis at the endomyocardial biopsy. In 2 families the relatives had a right ventricular cardiomyopathy. The mode of inheritance was autosomal dominant in 7 families, recessive in 4 and probably X-linked in 1. Familial transmission is not rare. The various forms of genetic transmission and manifestations of myocardial diseases in the same family suggest that familial DC is a multifactorial syndrome.

MISCELLANEOUS

1454

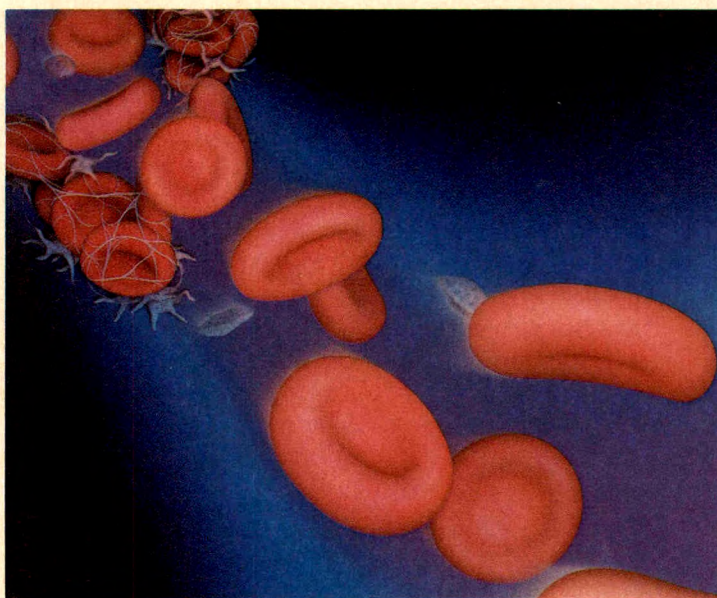
Influence of Aging on Pulmonary Hemodynamics in a Population Free of Coronary Artery Disease

William R. Davidson and Eric C. Fee

We sought to determine the influence of aging on pulmonary hemodynamics in subjects without angiographically demonstrable coronary disease or left ventricular systolic dysfunction (ejection fraction $\geq 50\%$ and

Continued on page A30

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References: 1. Faigel DJ, Jakubowski JA, Stampfer MJ, et al: Multiple doses of regular and enteric-coated aspirin produce equivalent platelet inhibitory effects. *Curr Ther Res* 1986; 39:519-527.

2. Demke DM, Luderer JR, Wakefield KL, et al: The effect of itazigrel and aspirin on the mucosa of the esophagus, stomach, and duodenum of normal subjects. *J Clin Pharmacol* 1987; 27: 916-920.

3. Data on file, SmithKline Consumer Products, a SmithKline Beckman Company.

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left ventricular end-diastolic pressure <14 mm Hg). Forty-seven normal subjects were identified out of 5,508 consecutive cardiac catheterizations. In group I (age ≥ 60 years), mean pulmonary artery pressure (16 ± 3 mm Hg), vascular resistance (124 ± 32 dynes s cm^{-5}) and pulmonary/systemic resistance ratio (0.099 ± 0.046) were higher than in group II (age <60 years) at 12 ± 2 mm Hg, 70 ± 25 dynes s cm^{-5} and 0.057 ± 0.019 , respectively (all p values <0.01 to 0.001). All pulmonary hemodynamic variables increased linearly with age. This increase is not due to occult coronary disease or ventricular systolic dysfunction, factors that have not been adequately excluded in previous studies.

1459

Prognostic Value of Intravenous Dipyridamole Thallium Imaging in Patients with Diabetes Mellitus Considered for Renal Transplantation

Alan D. Camp, Paul J. Garvin, Judy Hoff, Jeanne Marsh, Sheila L. Byers, and Bernard R. Chaitman

Patients with diabetes and end-stage renal failure are known to have a high risk for cardiac morbidity and mortality associated with renal transplantation. The most efficient method to determine preoperative cardiac risk has not been established. To determine the effectiveness of intravenous dipyridamole thallium imaging in predicting cardiac events, 40 diabetic renal transplant candidates were studied preoperatively in a prospective trial. The study group consisted of 40 patients whose average age was 42 years (range 27 to 64); 34 (85%) were hypertensive and 21 (53%) were cigarette smokers. Dipyridamole thallium imaging demonstrated reversible defects in 9 patients, fixed defects in 8 patients and normal scans in 23 patients. Cardiac events occurred in 6 patients, all of whom had reversible thallium defects. The average duration of follow-up was 11 months (range 1 to 21). Thus, dipyridamole thallium imaging is an effective method of identifying renal transplant candidates likely to develop cardiac complications. Routine coronary angiography may not be necessary to screen all renal transplant candidates for coronary artery disease before surgery.

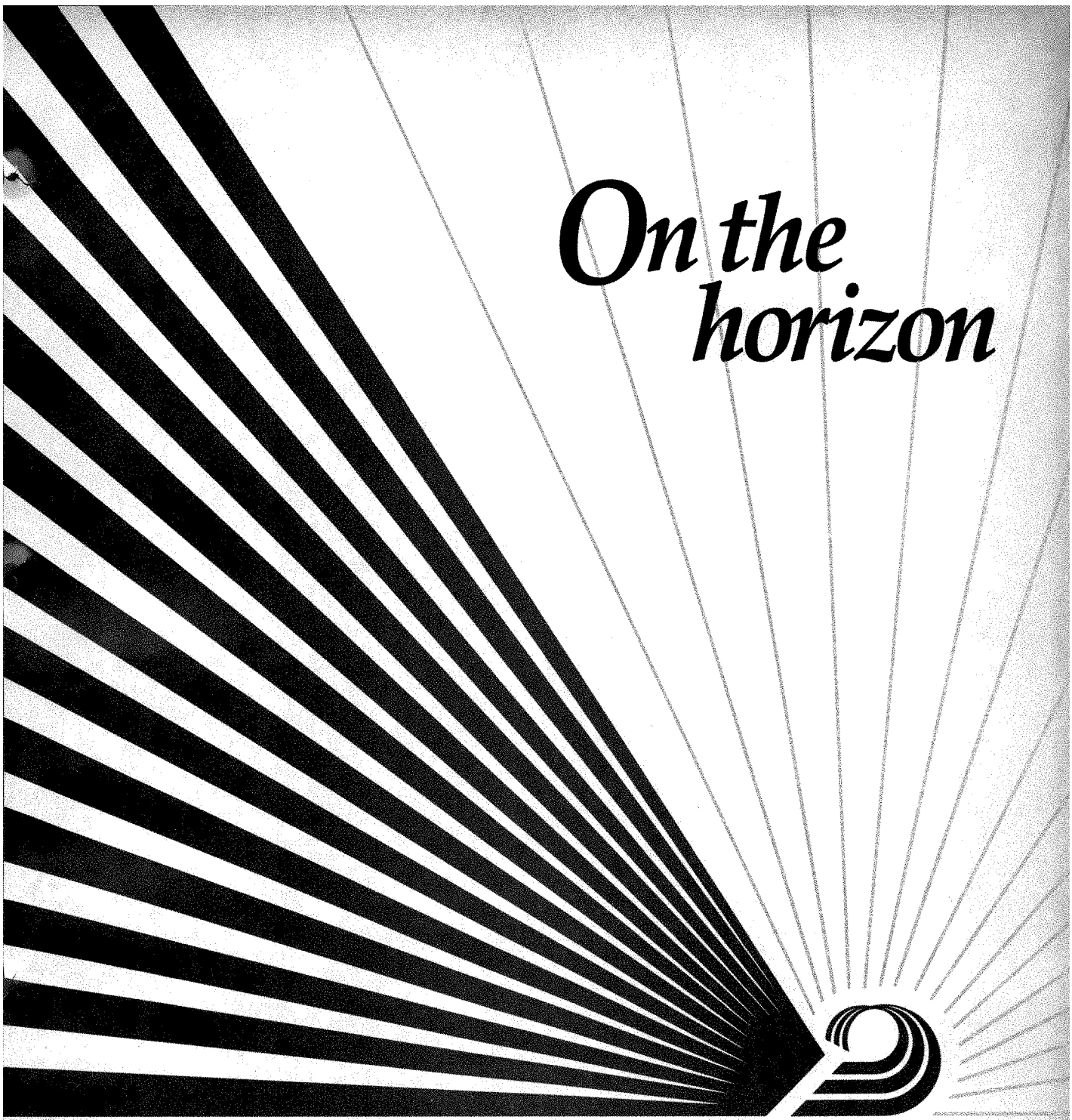
1464

Superior Vena Cava Doppler Flow Velocity Patterns in Pericardial Disease

Benjamin F. Byrd, III, and Ryk W. Linden

Superior vena cava (SVC) Doppler ultrasound was used to study 8 normal adults and 34 patients with known pericardial disease. First expiratory diastolic flow velocities (D_{fe}) in the SVC were quantitated for the first time and did not differ significantly in normal subjects and patients with hemodynamically insignificant pericardial effusions (23 ± 3 cm/s and 29 ± 13 cm/s, difference not significant). D_{fe} was less than 15 cm/s only in the patients with cardiac tamponade (9 ± 3 cm/s, $p < 0.01$). Constrictive pericarditis was distinguished from all other groups by a ratio of systolic to diastolic flow velocity ≤ 1.1 in the first expiratory beat ($p < 0.01$), although not from restrictive cardiomyopathy. Quantitative analysis of SVC flow velocity patterns is a useful addition to the echocardiographic evaluation of pericardial disease.

Continued on page A32



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1471

Transient Alterations in Cardiac Performance After a Six-Hour Race

Ignasi Carrió, Ricard Serra-Grima, Lluís Berná, Montserrat Estorch, Carlos Martínez-Duncker, and Jordi Ordoñez

Ten long distance runners were enrolled in a 6-hour competitive race. Immediately after the race technetium-99m-albumin gated blood pool scans were performed and indium-111 antimyosin was injected. Forty-eight hours later antimyosin scans were obtained and control gated blood pool scans were performed. Left ventricular ejection fraction was higher after the race (65 ± 5 vs $60 \pm 7\%$, $p < 0.01$) due to a decrease in end-systolic counts. Right ventricular ejection fraction was lower after the race (42 ± 7 vs $54 \pm 12\%$, $p = 0.03$) due to an increase in both end-diastolic and end-systolic counts. A longer systolic period was observed after the race ($53 \pm 5\%$ of the RR interval vs $39 \pm 3\%$, $p = 0.005$). No significant differences were observed in peak filling or peak emptying rates after the race. An increase in pulmonary blood volume (116% of control) was observed after the race. Antimyosin scans were normal in 7 athletes and minimal antimyosin myocardial uptake was seen in 3.

1475

The Electrocardiogram at Rest and Exercise During a Simulated Ascent of Mt. Everest (Operation Everest II)

Mark Malconian, Paul Rock, Herbert Hultgren, Howard Donner, Allen Cymerman, Bertron Groves, John Reeves, James Alexander, John Sutton, Masao Nitta, and Charles Houston

Electrocardiograms were recorded in 8 normal young men at rest and during maximal cycle ergometer exercise at several simulated altitudes up to 8,848 m during a 40-day stay in a hypobaric chamber. Resting electrocardiographic changes were first evident at 3,660 m and consisted of an increase in heart rate, right-axis deviation and other changes compatible with pulmonary hypertension, which was present in all subjects. Maximal exercise at 7,620 and 8,848 m was not associated with any ST-T-wave changes that could be attributed to ischemia or myocardial dysfunction despite respiratory alkalosis and severe hypoxemia.

1481

Thrombotic and Cardiovascular Complications Related to Nonionic Contrast Media During Cardiac Catheterization: Analysis of 8,517 Patients

Charles J. Davidson, Daniel B. Mark, Karen S. Pieper, Katherine B. Kisslo, Mark A. Hlatky, Don A. Gabriel, and Thomas M. Bashore

Thrombotic and cardiovascular complications were prospectively evaluated in 8,517 consecutive patients undergoing diagnostic cardiac catheterization with nonionic contrast media. Thrombotic events occurred in 15 patients (0.18%), 7 of whom had a coronary artery thrombus or embolus. Six of the 15 patients were premedicated with heparin. Thrombotic events tended to occur in clusters within short time intervals. Other cardiovascular complications were low with an incidence of ventricular tachycardia/

Continued on page A38

Rythmol

propafenone HCl
150 mg and 300 mg scored tablets

INDICATIONS AND USAGE

RYTHMOL (propafenone HCl) is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgement of the physician, are life threatening. Because of the proarrhythmic effects of RYTHMOL, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. The use of RYTHMOL is not recommended for use in patients with less severe ventricular arrhythmias, even if the patients are symptomatic. Use of RYTHMOL for the treatment of sustained ventricular tachycardia, like other antiarrhythmics, should be initiated in the hospital.

CONTRAINDICATIONS

RYTHMOL (propafenone HCl) is contraindicated in the presence of uncontrolled congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation and/or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, manifest electrolyte imbalance, and known hypersensitivity to the drug.

WARNINGS:

Mortality: In the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double blind study in patients with asymptomatic non life threatening ventricular ectopy who had a myocardial infarction more than six days but less than two years previously and demonstrated mild to moderate left ventricular dysfunction, an excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to carefully matched placebo treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months. The applicability of these results to other populations (e.g., those without recent myocardial infarction and to other antiarrhythmic drugs) is uncertain, but at present it is prudent (1) to consider any IC agent (especially one documented to provoke new serious arrhythmias) to have a similar risk and (2) to consider the risks of Class IC agents, coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life threatening, symptoms or signs.

Proarrhythmic Effects

RYTHMOL, like other antiarrhythmic agents, may cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., tachycardia that is more sustained or more rapid which may lead to fatal consequences. It is therefore essential that each patient given RYTHMOL be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to RYTHMOL (propafenone HCl) supports continued treatment. Overall in clinical trials with propafenone, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had a worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias, which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see above) suggests that an increased risk is present throughout treatment.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE PROPAFENONE or other agents with beta adrenergic blocking activity.

Congestive Heart Failure

During treatment with oral propafenone in patients with depressed baseline function (mean EF=33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients; of those 0.9% were considered probably or definitely related to RYTHMOL. Of the patients with congestive heart failure probably related to propafenone, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to RYTHMOL developed rarely (<0.2%) in patients who had no previous history of CHF. As RYTHMOL exerts both beta blockade and a (dose related) negative inotropic effect on cardiac muscle, patients with congestive heart failure should be fully compensated before receiving RYTHMOL. If congestive heart failure worsens, RYTHMOL should be discontinued (unless congestive heart failure is due to the cardiac arrhythmia) and, if indicated, restarted at a lower dosage only after adequate cardiac compensation has been established.

Conduction Disturbances

RYTHMOL slows atrioventricular conduction and also causes first degree AV block. Average PR interval prolongation and increases in QRS duration are closely correlated with dosage increases and concomitant increases in propafenone plasma concentrations. The incidence of first degree, second degree, and third degree AV block observed in 2,127 patients was 2.5%, 0.6%, and 0.2%, respectively. Development of second or third degree AV block requires a reduction in dosage or discontinuation of RYTHMOL. Bundle branch block (1.2%) and intraventricular conduction delay (1.1%) have been reported in patients receiving propafenone. Bradycardia has also been reported (1.5%). Experience in patients with sick sinus node syndrome is limited and these patients should not be treated with propafenone.

Effects on Pacemaker Threshold

RYTHMOL may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

Hematologic Disturbances

One case of agranulocytosis with fever and sepsis, probably related to use of propafenone, was seen in U.S. clinical trials. The agranulocytosis appeared after 8 weeks of therapy. Propafenone therapy was stopped and the white count had normalized by 14 days. The patient recovered. In the course of over 800,000 patient years of exposure during marketing outside the U.S. since 1978, seven additional cases have been reported. In one of these, concomitant captopril, a drug known to cause agranulocytosis, was used. Unexplained fever and/or decrease in white cell count, particularly during the first three months of therapy, warrant consideration of possible agranulocytosis/granulocytopenia. Patients should be instructed to promptly report the development of any signs of infection such as fever, sore throat, or chills.

PRECAUTIONS

Hepatic Dysfunction:

Propafenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. The dose of propafenone given to patients with impaired hepatic function should be significantly reduced. Careful monitoring for excessive pharmacologic effects (see OVERDOSAGE) should be carried out.

Renal Dysfunction:

A considerable percentage of propafenone metabolites (18.5%-38% of the dose/48 hours) are excreted in the urine. Until further data are available, RYTHMOL should be administered

cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (see OVERDOSAGE).

Elevated ANA Titers:

Positive ANA titers have been reported in patients receiving propafenone. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

Impaired Spermatogenesis:

Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose intravenous administration. Evaluation of the effects of short term propafenone administration on spermatogenesis in 11 normal subjects suggests that propafenone produced a reversible, short term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving propafenone chronically have suggested no effect of propafenone on sperm count.

Drug Interactions: Quinidine: Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers. There is, as yet, too little information to recommend concomitant use of propafenone and quinidine. **Local Anesthetics:** Concomitant use of local anesthetics may increase the risks of central nervous system side effects. **Digitalis:** RYTHMOL produces dose related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day propafenone without affecting digoxin renal clearance. Digoxin dosage should ordinarily be reduced when propafenone is started. **Beta-Antagonists:** Propafenone appears to inhibit the hydroxylation pathway for propranolol and metoprolol (just as quinidine inhibits propafenone metabolism). While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone. **Warfarin:** In a study of eight healthy subjects receiving propafenone and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary. **Cimetidine:** Concomitant administration of propafenone and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone.

Other: Limited experience with propafenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Life time maximally tolerated oral dose studies in mice (up to 360 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propafenone. RYTHMOL was not mutagenic when assayed for genotoxicity. **Pregnancy Teratogenic Effects:** Pregnancy Category C: Propafenone has been shown to be embryotoxic in rabbits and rats when given in doses 10 and 40 times, respectively, the maximum recommended human dose. No teratogenic potential was apparent in either species. There are no adequate and well controlled studies in pregnant women. Propafenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Pregnancy Nonteratogenic Effects:** In a perinatal and postnatal study in rats, propafenone, at dose levels of 6 or more times the maximum recommended human dose, produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development. **Labor and Delivery:** It is not known whether the use of propafenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from RYTHMOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of RYTHMOL in children has not been established.

Geriatric Use: There do not appear to be any age-related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, RYTHMOL should be used with caution. The effective dose may be lower in these patients.

Adverse Reactions: Adverse reactions associated with RYTHMOL (propafenone HCl) occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. About 20% of patients discontinued due to adverse reactions.

Adverse reactions reported for $\geq 1\%$ of 2,127 patients who received propafenone in U.S. clinical trials are presented in the following list. Dizziness, Nausea and/or Vomiting, Unusual Taste, Constipation, Fatigue, Dyspnea, Proarrhythmia, Angina, Headache(s), Blurred Vision, CHF, Ventricular Tachycardia, Dyspepsia, Palpitations, Rash, First Degree AV Block, Diarrhea, Weakness, Dry Mouth, Syncope/Near Syncope, Increased QRS Duration, Chest Pain, Anorexia, Abdominal Pain/Cramps, Ataxia, Insomnia, Premature Ventricular Contraction(s), Bradycardia, Anxiety, Edema, Tremor(s), Diaphoresis, Bundle Branch Block, Drowsiness, Atrial Fibrillation, Flatulence, Hypotension, Intraventricular Conduction Delay, Joint(s) Pain.

In addition, the following adverse reactions were reported less frequently than 1% either in clinical trials or in marketing experience (*adverse events for marketing experience are given in italics*). Causality and relationship to propafenone therapy can not necessarily be judged from these events. **Cardiovascular System:** Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia. **Nervous System:** Abnormal dreams, abnormal speech, abnormal vision, *apnea*, coma, confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo. **Gastrointestinal:** A number of patients with liver abnormalities associated with propafenone therapy have been reported in foreign postmarketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were, simply discovered through clinical chemistries, others because of clinical symptoms. One case was rechallenged with a positive outcome. Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), gastroenteritis, hepatitis (0.03%). **Hematologic:** Agranulocytosis, anemia, bruising, granulocytopenia, increased bleeding time, leukopenia, purpura, thrombocytopenia. **Other:** Alopecia, eye irritation, hyponatremia/inappropriate ADH secretion, impotence, increased glucose, kidney failure, positive ANA (0.7%), lupus erythematosus, muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus.

OVERDOSAGE

The symptoms of overdosage, which are usually most severe within 3 hours of ingestion, may include hypotension, somnolence, bradycardia, intraatrial and intraventricular conduction disturbances, and rarely convulsions and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam. General supportive measures such as mechanical respiratory assistance and external cardiac massage may be necessary.

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ventricular fibrillation of 0.1%, profound bradycardia 0.2% and prolonged angina 0.3%. Although thrombotic events have unusual temporal clustering and result in major complications, the overall incidence is low and comparable to previous studies using ionic contrast agents.

METHODS**1485**

Comparison with Radionuclide Angiography of Two New Geometric and Four Nongeometric Models for Echocardiographic Estimation of Left Ventricular Ejection Fraction Using Segmental Wall Motion Scoring

Robert D. Rifkin and Hitoshi Koito

Two-dimensional echocardiography was used to visually score wall motion in 12 regions of the left ventricle. Two methods for determining ejection fraction from these scores were compared to radionuclide angiography in 50 patients. In method 1, scores were converted to systolic dimensional changes. Using standard geometric considerations, global ejection fraction was calculated from the average of the individual ejection fractions of the 4 quadrants in the proximal, and the 4 quadrants in the distal left ventricle. Correlation with radionuclide ejection fraction was 0.917. In method 2, a simple linear combination of the mean wall motion score at the base, midleft ventricle and apex was used to estimate ejection fraction. After correction by regression, correlation with radionuclide angiography was 0.910 with this method. Therefore, wall motion scoring using an appropriate scale and geometric model provides good estimates of ejection fraction if ventricular quadrants are analyzed separately. Properly weighted linear combinations of the same scores may provide comparably accurate estimates of ejection fraction.

1491

Measurement of Intracardiac Dimensions and Structures in Normal Young Adult Subjects by Transesophageal Echocardiography

Michael Drexler, Raimund Erbel, Udo Müller, Norbert Wittlich, Susanne Mohr-Kahaly, and Jürgen Meyer

Standardized measurements of well-defined transesophageal cross-sectional planes were performed in 25 healthy volunteers. The left ventricular short-axis view and the 2- or 4-chamber view with the left and right atrium, the long axis of the left and right ventricle, the mitral and tricuspid valve ring and the atrial septum were analyzed in end-diastole and end-systole. Furthermore, the aortic valve plane, the diameters of the ascending and descending aorta and the pulmonary artery stem and the right pulmonary artery were also measured.

Continued on page A40

SINGLE-AGENT SUCCESS IN

OF HYPERTENSIVE PATIENTS*1-6

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see Warnings), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdose. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with α_1 -adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digoxin toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 74 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability.

Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia, HR < 50/min (1.4%), AV block, total 1°/2°/3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

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*In mild to moderate hypertension.

AP0-W1121

†Lower initial doses of 120 mg a day may be warranted in patients who may have an increased response to verapamil (eg, the elderly or small people).

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The Prehospital Phase of Acute Myocardial Infarction in the Era of Thrombolysis

Stanley B. Schmidt, MD, and Mark A. Borsch, MD

To evaluate the factors affecting the time between symptom onset and hospital arrival in patients with acute myocardial infarction (AMI), we gave a detailed questionnaire to all who were admitted or transferred with AMI from January 1988 to February 1989. In these 126 patients (94 men, 32 women) the mean prehospital time was 5.9 ± 11.0 hours (median 2.0, range 0.4 to 69.0). The time between symptom onset and reaching a decision that medical care should be sought was 62% of the mean prehospital time. In 100 (79%) patients, the prehospital time was ≤ 6 hours; of these, 61 (61%) were retrospectively judged to have been optimal candidates for lytic therapy. Stepwise multiple regression selected the following 4 variables as independent predictors of prehospital time: slow symptom progression; low income; female gender; and advanced age. All of these variables are predictive ($p < 0.03$) of increased prehospital time; absence of prior AMI was of borderline additional significance ($p = 0.053$). Similarly, logistic regression analysis selected slow symptom progression, female gender and low income as significant ($p \leq 0.02$) independent predictors of prehospital time > 6 hours. The logistic regression model incorporating these 3 variables had a sensitivity of 54%, a specificity of 95% and a positive predictive value of 72% in identifying patients with prehospital time > 6 hours. Thus, these data indicate it is possible to characterize patients likely to experience undue prehospital delay during AMI, which may be of importance to future public education efforts.

(Am J Cardiol 1990;65:1411-1415)

Prompt treatment of patients with acute myocardial infarction (AMI) decreases death from early arrhythmia and maximizes the potential benefit of thrombolytic therapy. Both the Italian Group for the Study of Streptokinase in Myocardial Infarction and the Second International Study of Infarct Survival showed strong associations between the promptness of treatment and the amount of decrease in AMI mortality using intravenous streptokinase.^{1,2} In the Italian study, no advantage was shown to lytic therapy when delayed beyond 6 hours after symptom onset. While some patients who present late may be found to benefit from thrombolysis,³ the time to treatment will remain a critical determinant of therapeutic outcome. Unfortunately, clinical experience shows that many patients with AMI continue to arrive relatively late after development of symptoms. This study evaluates the factors affecting the time between symptom onset and hospital arrival in patients with AMI to determine if a profile can be developed of those most likely to exhibit undue delay in seeking medical care.

METHODS

Study patients: The study sample consisted of 161 patients admitted or transferred to our medical center between January 1988 and February 1989 with out-of-hospital AMI. Those who agreed to participate were given a detailed questionnaire supplemented by chart review to determine factors affecting prehospital time and subsequent hospital course. The study was purely observational and was not designed to affect patient evaluation or treatment. Reasons for exclusion in 35 (22%) patients were death before completion of the survey (23 patients), painless AMI (2), patient refusal (1) and miscellaneous (9), leaving 126 patients (78%) in the final study sample. Admitted (42, 33%) and transferred (84, 67%) patients were similar in regard to most variables and were grouped together for subsequent data analysis. Confirmation of AMI required a peak serum creatine kinase of $\geq 150\%$ of the laboratory's upper normal value, in addition to conventional clinical and/or electrocardiographic criteria.

Definitions: Precall time was the interval between symptom onset and calling to be taken to a hospital. It was subdivided into the following: a notification time, extending from symptom onset to notification of another person of the presence of symptoms; a decision time, extending from the time of symptom notification to the time a decision was made that medical care should be

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TABLE 1 Time Periods in Early and Late Arrival Groups

Time Period	Early Group n = 100 (h)	Late Group n = 26 (h)	p Value
Notification	0.7 ± 1.2	5.1 ± 7.1	0.0080
Decision	0.5 ± 0.9	13.9 ± 21.9	0.0006
Delay	0.1 ± 0.2	1.4 ± 3.4	NS
Wait	0.3 ± 0.4	0.2 ± 2.5	NS
Travel	0.6 ± 0.5	0.5 ± 0.4	NS
Precall	1.3 ± 1.4	20.4 ± 19.4	<0.0001
Prehospital	2.2 ± 1.5	21.1 ± 19.3	<0.0001

NS = not significant.

sought; and a delay time, which comprised the interval between reaching a decision care should be sought and calling for hospital transportation.

Wait time extended from summoning transportation to leaving for a hospital and transportation time was the time between leaving for and arriving at a hospital.

Prehospital time comprised the total period between symptom onset and hospital arrival. Patients were divided into early and late arrival subgroups based on prehospital time $\leq$ or >6 hours, respectively. Some time periods did not apply or could not be determined in some patients. Prehospital time, however, was recorded for every patient.

Denial was scored as present if patients agreed with the statement, "I have not been afraid during this heart attack."⁴

Suppression was scored as present if patients agreed with the statement, "I tried not to think about my symptoms."⁴

Locus of control⁵ was measured as the sum of scores on 7 items, 4 of which dealt specifically with control of personal health (e.g., "most people cannot do much to influence their health"). Scores were determined using the following point scale: agree strongly = 1; agree somewhat = 2; disagree somewhat = 3; disagree strongly = 4. Possible scores ranged from 7 (maximum external locus of control) to 28 (maximum internal locus of control).

Depression was measured as the sum of scores on 4 items taken from the Zung self-rating depression scale.⁶

Possible scores ranged from 4 (least depressed) to 16 (most depressed). In a separate validation sample of nonhospitalized volunteers, the responses to these 4 items correlated well with the total 20-item Zung depression scale score ($r_s = 0.85$, $p = 0.0002$).

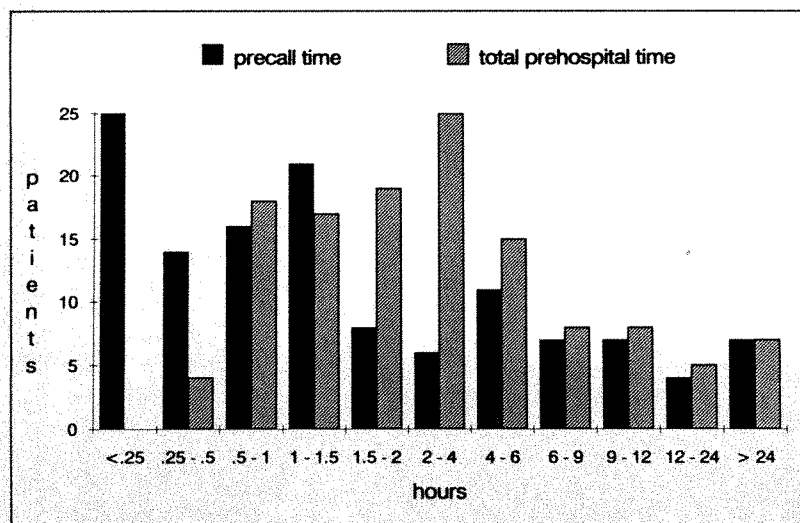
Patency of the infarct artery was defined as when coronary angiography done within 12 hours of symptom onset showed grade 2 or 3 perfusion of the presumed infarct artery.⁷ Participation in the study did not affect the performance or timing of coronary angiography or other procedures. Patients were retrospectively considered to be optimal lytic therapy candidates if they met the following criteria: pain ≤ 6 hours; age <80 years; Thrombolysis in Myocardial Infarction Trial electrocardiographic criteria⁷; and absence of strong contraindications³ to treatment. As this was not a study of thrombolytic therapy *per se*, no uniform prospective indications for lytic therapy existed.

AMI complications were scored as present if the patient developed congestive heart failure, post-AMI angina, cardiogenic shock, or if he or she required a pacemaker, Swan-Ganz catheter or readmission to the coronary care unit.

Data analysis: Group frequencies were compared by chi-square test and group means were compared by Mann-Whitney tests. Spearman correlation coefficients were calculated for selected pairs of continuous variables. Time of symptom onset was analyzed after angular transformation of data.⁸ The multivariable procedures that were performed were forward stepwise regression analysis of total prehospital time and logistic regression analysis of total prehospital time ≤ 6 or >6 hours. Mean values are expressed as $\pm$ standard deviation. A p value <0.05 was considered statistically significant.

RESULTS

Time periods: The frequency distributions of precall and prehospital times are shown in Figure 1. The mean precall time was 5.1 ± 11.1 hours (median 1.1, range 0 to 68.5) and the mean prehospital time was 5.9 ± 11.0 hours (median 2.0, range 0.4 to 69.0). Precall time correlated closely with total prehospital time ($r_s = 0.91$, p

**FIGURE 1.** Precall and total prehospital times.

<0.0001). In 100 (79%) patients, the prehospital time was ≤ 6 hours (early arrival group); in the remaining 26 (21%) patients, the prehospital time was >6 hours (late arrival group). Time periods for the early and late arrival groups are listed in Table I. The longer prehospital time in the late group was largely accounted for by much longer notification and decision periods, which together accounted for 90% of prehospital time in the late group compared to 54% in the early group ($p = 0.0001$). The delay, wait and transportation periods did not differ significantly between the 2 groups.

Univariate analysis of early and late arrival subgroups: Further characteristics of the early and late arrival groups are listed in Table II. Female gender, low income, advanced age, slow symptom progression and history of hypertension were all significant univariate predictors of greater prehospital delay. Low intensity of initial symptoms was of borderline significance ($p = 0.05$). Women were almost twice as likely as men to report a history of hypertension (69 vs 35%, $p = 0.001$) and this probably accounts for the observed univariate association between hypertension and prehospital delay. Only 2 (6%) of the 31 patients with prior AMI had previously received thrombolytic therapy; both were in the early arrival group (difference not significant).

Several time variables were analyzed, including the month, day and hour of symptom onset. These time variables, as well as weekend versus weekday onset of symptoms, did not differ significantly between the early and late groups.

In response to questions about the nature of patients' initial symptoms, 22 (17%) denied chest "pain" or chest "discomfort" and 19 (15%) denied the presence of initial pain in any body area. The frequency of the absence of these symptoms was similar in the early and late arrival groups. There were 34 (27%) patients who reported deciding "almost from the start" that their symptoms were "probably due to a heart attack," but the proportion of patients reaching such a decision did not differ significantly between the early and late groups.

An attempt was made to contact a physician by 43 (34%) patients before hospital transport and late group patients were significantly more likely to make such an attempt ($p = 0.002$). Of these, 8 went to their doctor's office before going to a hospital and 7 did so on their physician's advice. The time spent in the physician's office averaged 45 ± 22 minutes and ranged from 20 to 90 minutes.

Outcome data: Outcome data are listed in Table III. Aside from the expected greater use of thrombolytic therapy in patients who arrived within 6 hours of symptom onset, no important differences in outcome variables were demonstrated between early and late arrival groups. The location of infarction was inferior in 58 patients (46%), anterior in 43 (34%), lateral in 6 (5%) and indeterminate in 19 (15%). Infarct location did not differ significantly between the early and late groups.

All lytic therapy was given intravenously and consisted of either tissue-type plasminogen activator (39 of 47 patients, 83%) or streptokinase (8 of 47, 17%). In patients given lytic therapy, the mean time to drug administration was 3.7 ± 2.3 hours after symptom onset

TABLE II Characteristics of Early and Late Arrival Groups

	Early Group n = 100	Late Group n = 26 (%)	p Value
Demographic			
M/F	82/18	12/14	0.001
Age (yrs)	56.4 ± 13	63.7 ± 13	0.01
Married	72	17 (65)	NS
Income $< \$10,000$ /yr	42	17 (65)	0.03
Health insurance	87	23 (88)	NS
Rural area	38	8 (31)	NS
History			
Angina	18	5 (19)	NS
AMI	24	7 (27)	NS
Coronary angiography	20	6 (23)	NS
Bypass surgery	5	2 (8)	NS
Diabetes mellitus	17	9 (35)	NS
Systemic hypertension	38	17 (65)	0.01
Cigarette smoking	83	16 (62)	NS
Family history	52	19 (73)	0.05
Medical care			
Physician	77	22 (85)	NS
Cardiologist	26	10 (38)	NS
Setting			
Alone	21	7 (27)	NS
At home	69	22 (85)	NS
At work	12	2 (8)	NS
Hour of onset	$6:05 \pm 3.6$ hr	$6:25 \pm 4$ hr	NS
Symptoms			
Chest pain	67	14 (54)	NS
Intensity (1 to 3)*	2.1 ± 0.8	1.7 ± 0.9	0.05
Progression (1 to 6)*	2.4 ± 1.1	3.8 ± 1.9	0.002
Response			
Self-treatment	53	14 (54)	NS
Called physician	27	16 (61)	0.002
Transport			
Ambulance	42	9 (35)	NS
Distance (1 to 3)*	2.4 ± 0.6	2.5 ± 0.7	NS
Knowledge			
Lytic therapy (0 to 3)*	0.9 ± 0.9	0.8 ± 1.1	NS
Early treatment (0 to 2)*	1.8 ± 0.5	1.8 ± 0.5	NS
Risk factors (0 to 6)*	4.2 ± 1.9	4.2 ± 1.8	NS
Psychologic			
Denial	25	8 (31)	NS
Suppression	15	5 (19)	NS
Locus of control (7 to 28)*	21.2 ± 4.5	19.4 ± 6.1	NS
Depression score (4 to 16)*	6.9 ± 2.4	7.3 ± 3.0	NS

* Potential range of scores.

AMI = acute myocardial infarction; Intensity = initial intensity of symptoms (1 = mild, 3 = severe); Medical care = current care by physician or cardiologist; NS = not significant; Progression = speed of symptom progression (1 = rapid, 6 = slow); Setting = circumstances of symptom onset.

and 1.6 ± 0.8 hours after hospital arrival. A nondiagnostic electrocardiogram was cited as the reason for withholding lytic therapy in 27 of 54 (50%) early group patients who did not receive thrombolysis. "Prolonged" prehospital time (4.2 ± 0.8 hours) and advanced age (82.1 ± 4.0 years) were cited as reasons for withholding treatment in 3 (6%) cases each and miscellaneous contraindications were present in 11 (20%); several patients were felt to have >1 contraindication to treatment. No apparent reason for withholding lytic therapy was present in 13 (24%) early group patients who did not receive lytic treatment. Of these, 12 (92%) were initially treated at outside referring hospitals, 9 (69%) had anterior AMI and only 1 lacked health insurance. The 1 patient in the late arrival group who received lytic therapy was a 39-year-old man who experienced a stuttering course of symptoms over a 15-hour-period before hospital arrival.

TABLE III Outcome Data

	Early Group n = 100	Late Group n = 26 (%)	p Value
ER pain	91	20 (77)	NS
ER systolic BP (mm Hg)	145 ± 30	139 ± 24	NS
ER CK (IU/liter)	119 ± 353	540 ± 641	0.01
Peak CK (IU/liter)	2058 ± 1994	1190 ± 820	0.03
Q-wave infarct	76	17 (65)	NS
AMI complication	55	12 (46)	NS
Optimal lytic candidate	61	0	<0.0001
Lytic therapy	46	1 (4)	0.0003
Lytic success	30/44 (68%)	0/1	NS
CCU days	3.7 ± 1.6	4.0 ± 2.6	NS
Coronary angiography	82	18 (69)	NS
Acute PTCA	11	1 (4)	NS
Bypass surgery	18	1 (4)	NS

AMI = acute myocardial infarction; BP = blood pressure; CCU = coronary care unit; CK = creatine kinase; ER = emergency room; PTCA = coronary balloon angioplasty.

TABLE IV Stepwise Linear Regression Analysis

Dependent variable: total prehospital time					
Step	Variable	F	B	SE of B	p Value
1	Progression	68.00	3.29	0.54	<0.0001
2	Income	10.03	-1.88	0.77	0.016
3	Gender	2.72	-4.13	1.87	0.029
4	Age	3.57	0.08	0.03	0.027
5	Prior AMI	3.81	-2.58	1.32	0.053
Multiple R = 0.688					
Multiple R-square = 0.474					
F = 19.83 DF = 5,110 p <0.00001					

AMI = acute myocardial infarction; B = sample partial regression coefficient; DF = degrees of freedom; F = variance ratio; R = regression coefficient; R-square = coefficient of determination; SE = standard error.

In this study, patients were interviewed 5.9 ± 3.5 days after their AMI, generally after transfer from the coronary care unit, and those who died before being surveyed were excluded from analysis. Mortality was therefore low, with only 1 in-hospital death observed.

Multivariable analyses: Results of forward stepwise regression analysis of total prehospital time are listed in Table IV. Slow symptom progression, low income, female gender and advanced age were all independently predictive ($p \leq 0.02$) of increased prehospital time. Absence of prior AMI was of borderline additional significance ($p = 0.053$). Similarly, logistic regression analysis selected slow symptom progression, female gender and low income as significant ($p \leq 0.02$) independent predictors of prehospital time >6 hours. The logistic regression model containing these 3 variables had a sensitivity of 54%, a specificity of 95% and a positive predictive value of 72% in identifying those who arrived >6 hours after symptom onset.

Patient perception of factors contributing to pre-hospital delay: At the end of the survey, patients were asked to report the factors which they felt added to their delay in reaching a hospital; 92 (73%) cited ≥ 1 contributing factor. Among these, the most frequently listed were the perception that "symptoms did not seem serious" (33 of 126 patients, 26%) and similarity of the AMI symptoms to past non-AMI symptoms (32, 25%). The advice of friends or family was cited as a factor

contributing to delay by 23 (18%) and 7 (6%) reported that concern about the cost of treatment contributed to their delay.

DISCUSSION

In this study, the strongest predictor of prehospital time was the pattern of symptom progression. Patients whose symptoms rapidly worsened exhibited little delay seeking medical care and had the shortest prehospital times. Demographic factors were also important with low income, female gender and advanced age all correlating with increased prehospital time. Prior AMI was a significant univariate predictor of (short) prehospital time and was of borderline significance in the linear regression analysis. The majority of total prehospital time was accounted for by the period between symptom onset and reaching a decision to seek medical care. Even in this largely rural population, the time spent being transported to a hospital was a relatively small fraction of total prehospital time.

Most previous studies of the prehospital phase of AMI antedate the widespread use of thrombolytic therapy.⁹⁻¹⁶ Many of these have included a mixture of patients with and without confirmed infarctions and have generally evaluated a limited number of potentially important variables. The pattern of symptom progression was examined only in the study by Alonzo,¹⁷ in which rapid symptom progression was identified as the variable most strongly associated with a short phase of self-evaluation of symptoms. Demographic variables have not been found to predict prehospital delay in most prior studies. Cooper et al¹⁸ evaluated prehospital delay in 111 black patients treated for AMI at Cook County Hospital in Chicago and observed a mean prehospital time of approximately 23 hours, which is considerably longer than in any other published study. While most of these late-arriving patients were poor enough to qualify for Medicaid (J. Ferlinz, MD, personal communication, October 1989), the association between income and prehospital delay was not directly examined.

Previous studies of prehospital delay have generally concluded with calls for further public education regarding the symptoms of AMI and the urgency of prompt medical evaluation. The results of this study may help direct future education to patient groups identified as currently being at particularly high risk for excessive prehospital delay. Two studies of broad educational campaigns have in fact shown that intense public education efforts can produce at least a short-term decrease in prehospital time among patients with AMI.^{19,20} The possible utility of a campaign directed specifically at groups identified as being at high risk for delay has not been examined.

The need for further physician education is supported by the observation that many early arrival patients who were retrospectively judged to have been good lytic therapy candidates were either not treated or were treated relatively late after hospital arrival. Other investigators have reported a similar degree of undertreatment²¹ and it is likely that this is a general problem not confined to unique geographic circumstances.

This study represents findings from 1 rural based medical center and the results may not be applicable to other regions with markedly different patient populations. Further work is needed to better define the impact of local conditions on prehospital delay. We did not observe any significant differences in patient characteristics or prehospital times between those who were brought directly to the university hospital and those initially treated at outlying community hospitals. It is also possible that our results have been affected by the exclusion of patients who died before being interviewed. Available chart data indicate that AMI patients who were admitted but died before being interviewed were generally similar to those who were surveyed, except for a higher proportion of women in the former group.

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Prediction of Preserved Flow to the Infarct Area Based on Admission Electrocardiogram in Anterior Wall Acute Myocardial Infarction

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To determine whether preserved flow to the infarct area could be predicted from the admission electrocardiogram and to define the effect of preserved flow on the late results after reperfusion, 20 anterior myocardial infarction patients who were successfully reperfused were studied. Patients were divided into 3 groups: (1) no-flow group (8 patients), with an occluded infarct-related artery and no easily visible collaterals; (2) intact collateral group (6 patients); and (3) subtotal obstruction group (6 patients). From the admission electrocardiogram, the sum of ST-segment elevation (Σ ST), the sum of R-wave amplitude (Σ R) in leads V_1 through V_6 and the ratio of these (Σ R/ Σ ST) were measured. There was no significant difference in Σ R among the 3 groups. The no-flow group had significantly lower Σ R/ Σ ST and higher Σ ST than the intact collateral group or subtotal obstruction group. All patients (6 of 6) with subtotal obstruction and all except 1 patient (5 of 6) with intact collateral showed Σ R/ Σ ST >2.5 or Σ ST <2.0 mV. All patients (8 of 8) with no flow showed Σ R/ Σ ST ≤ 2.5 and all except 1 patient with no flow (7 of 8) showed Σ ST ≥ 2.0 mV. The regional wall motion was assessed by the radial method at 4 weeks. The mean percentage systolic shortening in the anterior and apical regions was significantly correlated with Σ R/ Σ ST ($r = 0.75$, $p < 0.001$) and Σ ST ($r = -0.65$, $p < 0.005$).

Thus, the admission electrocardiographic finding of Σ R/ Σ ST >2.5 or Σ ST <2.0 mV indicated a preserved flow to the infarct area and relatively good regional wall motion in the convalescent stage after successful reperfusion in patients presenting with their first anterior wall acute myocardial infarction.

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The most effective way to limit the size of necrosis in acute myocardial infarction is early restoration of coronary artery flow. Many studies have demonstrated that reperfusion is beneficial if achieved within 4 hours of the onset of symptoms.¹⁻³ However, the interval between the onset of chest pain and the development of myocardial necrosis and Q waves on the electrocardiogram appears to be variable, because various degrees of preserved flow to the infarct area have a varied protective effect on myocardial cell death. Recanalization of the infarct-related coronary artery in the presence of preserved flow exerts a beneficial effect on left ventricular function even if achieved later than 6 hours after the onset of symptoms.⁴ Therefore, it is important not only to evaluate the duration of symptoms but also to predict preserved flow to the infarct area before initiating reperfusion therapy.

This study determines whether preserved flow (intact collaterals or subtotal obstruction) can be predicted from admission electrocardiographic findings in anterior wall acute myocardial infarction, and whether chronic phase regional wall motion after successful reperfusion can be predicted from the admission electrocardiogram.

METHODS

Study population: We studied 20 patients with anterior wall acute myocardial infarction (39 to 72 years old, mean 58) who met the following 3 criteria. (1) All patients had no history of prior myocardial infarction and had not experienced severe prolonged chest pain. All patients had no significant (luminal diameter stenosis $>70\%$) circumflex or right coronary artery stenosis. (2) There were no intraventricular conduction disturbances (QRS duration >0.12 second) on the admission electrocardiogram. (3) Reperfusion by coronary angioplasty was successful and there was no significant stenosis ($>70\%$) at 4 weeks. The diagnosis of acute myocardial infarction was based on the following 3 criteria: (1) presumed ischemic chest pain lasting at least 30 minutes; (2) ST-segment elevation of at least 0.1 mV measured 0.02 second after the J point in at least 2 precordial leads; and (3) significantly increased serum creatinine kinase followed by a subsequent reduction demonstrated retrospectively.

Measurement of electrocardiographic parameters: From a 12-lead electrocardiogram obtained immediately after hospital admission, the following parameters

were calculated. Σ ST was the sum of ST-segment elevation above the preceding T-P line 0.02 second after the J point in leads V_1 through V_6 . Σ R was the sum of R-wave amplitude in leads V_1 through V_6 . Σ R/ Σ ST was the ratio of these 2 parameters. ST-segment elevation and R-wave amplitude were measured to the nearest 0.05 mV.

Angiography and angioplasty procedures: After informed consent was obtained from patients or their families, emergency coronary arteriography was performed using Judkins technique. During the procedure, heparin 5,000 IU, nitroglycerin 0.1 to 0.5 μ g/kg/min and prophylactic xylocaine were administered intravenously. If necessary, morphine or diazepam was given. After an initial coronary arteriogram was obtained, intracoronary nitroglycerin 0.25 to 0.5 mg was infused into the infarct-related coronary artery. No patients had received intravenous thrombolytic therapy. Coronary angioplasty was performed with an 8Fr guiding catheter (Schneider), an 0.018-inch high torque floppy guidewire and a Simpson-Robert balloon catheter system (ACS). The balloon was advanced across the lesion and inflated for 30 to 180 seconds several times. Primary success of angioplasty was defined as achievement of a luminal diameter stenosis <70%.

Evaluation of baseline coronary arteriogram: According to the coronary arteriogram, patients were divided into 3 groups: (1) no-flow group (8 patients), (2) intact collateral group (6 patients) and (3) subtotal obstruction group (6 patients). No flow was defined as an infarct-related coronary artery totally occluded with no intact collaterals. Intact collateral was defined as the condition when not only branches but also the major trunk of the infarct-related coronary artery could be visualized through collaterals. Subtotal obstruction was defined as stenosis that permitted only markedly delayed filling of the distal artery. Patients with both subtotal obstruction and intact collaterals were included in the subtotal obstruction group. Intact collaterals or subtotal obstruction were considered preserved flow. Severe stenosis without delayed filling was considered adequate flow and was not included in this study.

Left ventricular wall motion analysis: From the left ventriculogram (30° right anterior oblique view) obtained 4 weeks after reperfusion, end-diastolic and end-systolic frames were selected during normal sinus beats and the endocardial borders were digitized. Radial lines from the center of the long axis were drawn clockwise every 5° from 30 to 300°, with the apex at 180°. The total systolic shortening of a segmental radius was calculated from the formula: percentage systolic shortening = $(D - S)/D \times 100$, where D was end-diastolic radius and S was end-systolic radius. Data for the percentage systolic shortening were derived by a computer system (Oscor, graphic digitizer U4-30 mark II and NEC, PC-9801) (Figure 1). The severity of the impairment of the segmental wall motion was evaluated by a modification of the method of Schröder et al.⁵ Radial axes with a percentage systolic shortening of <25% were defined as asynergy and those <10% were defined as akinesia. The severity of asynergy (asynergic index)

and the severity of akinesia (akinetic index) were calculated as shown in Figure 1. The anterior infarction area was considered to be 30 through 210°. The mean percentage systolic shortening within this area was calculated.

Statistical analysis: Data are presented as mean $\pm$ standard error. Statistical analysis was performed using Student *t* test. Linear regression equations were calculated to relate electrocardiographic parameters and regional wall motion. A *p* value <0.05 was considered significant.

RESULTS

Clinical features of the patients are listed in Table I. The prior incidence of hypertension was 45%, which was not significantly different among the 3 groups. No patient had any other condition that would cause left ventricular hypertrophy. Time to angioplasty from the

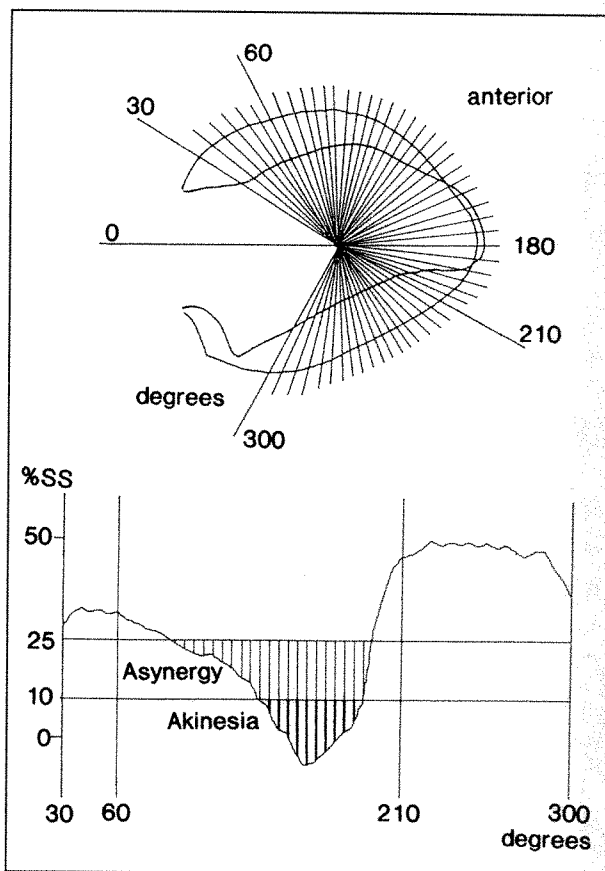


FIGURE 1. Analysis of the regional wall motion. Fifty-five radial axes were drawn from the center of the long axis (top). The percentage systolic shortening (%SS) of each radial axis was calculated and graphed (bottom). Radial axes with %SS <25% were defined as "asynergy." Also, radial axes with %SS <10% were defined as "akinesia." Thin lines were drawn every 5° within the closed area between the graphed line of the %SS and the horizontal 25% line. The severity of asynergy ("asynergic index") was calculated by the sum of the thin lines; the sum of (25 - %SS) of all asynergic axes. Also, thick lines were drawn every 5° within the closed area between the graphed line of %SS and the horizontal 10% line. The severity of akinesia ("akinetic index") was calculated by the sum of the thick lines; the sum of (10 - %SS) of all akinetic axes.

TABLE I Patient Characteristics

											Regional Wall Motion		
Patient No.	Age (yrs), Sex	HR (beats/min)	HT	ECG Parameters			CAG Findings			Time (hrs) to Angioplasty	Regional Wall Motion		
				ΣR	ΣST	$\Sigma R/\Sigma ST$	Lesion	Collateral	Subtotal		Asyn	Akin	Mean %SS
No-flow group													
1	44, F	120	0	0.10	5.90	0.02	seg 6	0	0	4.0	979	379	-3.9
2	66, M	90	+	2.10	4.30	0.49	seg 7	0	0	3.5	301	14	17.8
3	57, M	69	+	3.90	5.05	0.77	seg 7	0	0	2.5	331	106	16.6
4	68, F	75	+	6.80	5.20	1.31	seg 7	0	0	4.0	371	41	17.1
5	55, M	70	0	3.30	3.05	1.09	seg 6	0	0	4.0	341	4	15.2
6	65, M	66	0	5.60	2.60	2.15	seg 7	0	0	6.5	171	15	22.0
7	39, M	67	0	2.15	2.30	0.93	seg 6	0	0	3.5	213	0	19.3
8	57, M	95	+	0.20	1.20	0.17	seg 7	0	0	6.5	576	283	16.4
Intact collateral group													
9	43, M	95	0	3.45	1.35	2.56	seg 7	+	0	3.5	33	0	27.7
10	58, F	81	0	0.90	0.85	1.06	seg 7	+	0	10.0	496	55	10.3
11	51, M	59	0	7.45	0.75	9.93	seg 6	+	0	1.5	14	0	30.9
12	59, F	89	+	3.35	0.55	6.09	seg 6	+	0	6.5	147	0	22.1
13	59, M	65	+	6.40	0.50	12.8	seg 6	+	0	1.0	11	0	35.3
14	52, M	75	0	7.55	2.50	3.02	seg 6	+	0	2.0	36	0	32.6
Subtotal obstruction group													
15	68, F	70	+	4.05	0.65	6.23	seg 7	0	+	9.5	105	0	25.3
16	70, M	83	0	4.30	0.30	14.3	seg 7	0	+	3.5	52	0	36.6
17	70, M	71	+	7.80	1.50	5.20	seg 6	0	+	3.0	0	0	41.9
18	49, M	60	+	7.00	0.35	20.0	seg 7	+	+	9.0	1	0	38.0
19	56, M	68	0	2.45	0.45	5.44	seg 6	+	+	3.0	97	0	22.5
20	64, M	60	0	7.20	0.50	14.4	seg 6	0	+	4.5	0	0	39.7
Akin = akinetic index; Asyn = asynergic index; CAG = coronary arteriogram; Collateral = intact collateral; ECG = electrocardiogram; HR = heart rate; HT = history of hypertension; %SS = % systolic shortening; seg = segment; Subtotal = subtotal obstruction; + = present; 0 = absent.													

Akin = akinetic index; Asyn = asynergic index; CAG = coronary arteriogram; Collateral = intact collateral; ECG = electrocardiogram; HR = heart rate; HT = history of hypertension; %SS = % systolic shortening; seg = segment; Subtotal = subtotal obstruction; + = present; 0 = absent.

onset of symptoms was 4.6 ± 2.5 hours. There was no significant difference among the 3 groups (4.3 ± 1.3 hours in the no-flow group, 4.1 ± 3.2 hours in the intact collateral group and 5.4 ± 2.8 hours in the subtotal obstruction group).

Admission electrocardiographic parameters and coronary arteriographic findings: There was no significant difference in ΣR among the 3 groups (3.02 ± 2.23 mV in the no-flow group, 4.85 ± 2.46 mV in the intact collateral group and 5.47 ± 1.97 mV in the subtotal obstruction group) (Figure 2). The no-flow group showed significantly higher ΣST than the intact collateral group (3.70 ± 1.55 vs 1.08 ± 0.69 mV, $p < 0.005$) or the subtotal obstruction group (3.70 ± 1.55 vs 0.63 ± 0.41 mV, $p < 0.001$). The no-flow group showed signifi-

cantly lower $\Sigma R/\Sigma ST$ than the intact collateral group (0.87 ± 0.64 vs 5.91 ± 4.22 , $p < 0.01$) or the subtotal obstruction group (0.87 ± 0.64 vs 10.93 ± 5.64 , $p < 0.001$).

Coronary arteriographic findings and chronic phase regional wall motion: Asynergic index in the no-flow group was significantly higher than that in the intact collateral group (410 ± 243 vs 123 ± 173 , $p < 0.05$) or in the subtotal obstruction group (410 ± 243 vs 43 ± 45 , $p < 0.005$) (Figure 3). Akinetic index was not significantly different among the 3 groups (105 ± 136 in the no-flow group, 9 ± 20 in the intact collateral group and no akinetic axis in the subtotal obstruction group). Mean percentage systolic shortening in the no-flow group was significantly lower than that in the intact col-

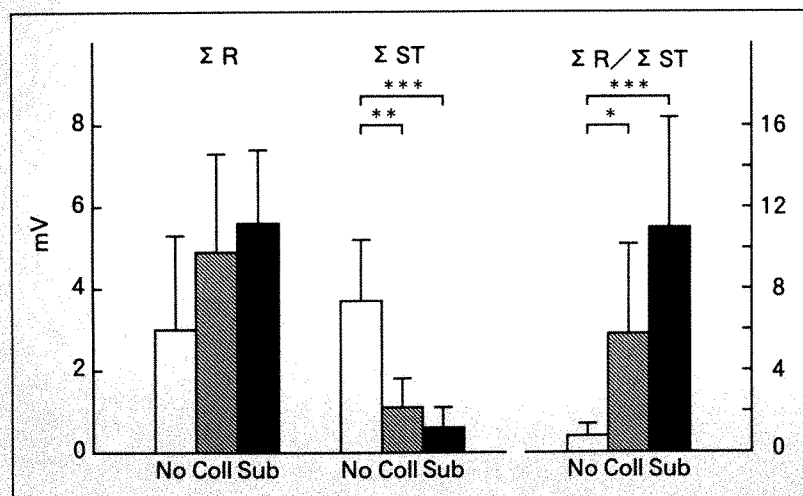


FIGURE 2. Admission electrocardiographic findings in relation to coronary arteriographic findings. Coll = intact collateral group; No = no-flow group; Sub = subtotal obstruction group; ΣR = the sum of R-wave amplitude in leads V_1 through V_6 ; ΣST = the sum of ST-segment elevation in leads V_1 through V_6 . * $p < 0.01$; ** $p < 0.005$; *** $p < 0.001$.

TABLE II Coronary Arteriographic Findings and Chronic Phase Regional Wall Motion in Relation to Admission Electrocardiographic Parameters

	$\Sigma R/\Sigma ST$		ΣST (mV)	
	≤ 2.5	> 2.5	≥ 2.0	< 2.0
Time to angioplasty (hrs)	4.9 ± 2.2	4.3 ± 2.7	3.8 ± 1.3	5.1 ± 3.0
Asynergic index	420 ± 230	$45 \pm 48^*$	343 ± 262	$128 \pm 189^{\dagger}$
Akinetic index	100 ± 129	$0 \pm 0^{\ddagger}$	70 ± 121	28 ± 78
Mean % SS	14.5 ± 7.2	$32.1 \pm 6.6^*$	17.1 ± 9.5	$28.9 \pm 9.5^{\S}$
Subtotal obstruction	0	6	0	6
Intact collateral	1	5	1	5
No flow	8	0	7	1

* $p < 0.001$ vs $\Sigma R/\Sigma ST \leq 2.5$; $^{\dagger} p < 0.02$ vs $\Sigma R/\Sigma ST \leq 2.5$; $^{\ddagger} p < 0.05$ vs $\Sigma ST \geq 2.0$; $^{\S} p < 0.02$ vs $\Sigma ST \geq 2.0$.
% SS = % systolic shortening.

lateral group ($15.1 \pm 7.4\%$ vs $26.5 \pm 8.3\%$, $p < 0.02$) or in the subtotal obstruction group ($15.1 \pm 7.4\%$ vs $34.0 \pm 7.4\%$, $p < 0.001$).

Admission electrocardiographic parameters and chronic phase regional wall motion: There was a significant correlation between ΣR and mean percentage systolic shortening ($r = 0.79$, $p < 0.001$); the correlation was especially good in patients with preserved flow ($r = 0.86$, $p < 0.001$) (Figure 4). The relation between ΣR and mean percentage systolic shortening in the no-flow group was poor, however. There was a significant negative correlation between ΣST and mean percentage systolic shortening ($r = -0.65$, $p < 0.005$). There was a significant positive correlation between $\Sigma R/\Sigma ST$ and mean percentage systolic shortening ($r = 0.75$, $p < 0.001$).

From the electrocardiographic parameters, no flow and preserved flow were clearly differentiated (Table II). All patients with subtotal obstruction (6 of 6) and all except 1 patient with intact collaterals (5 of 6) showed $\Sigma R/\Sigma ST > 2.5$ or $\Sigma ST < 2.0$ mV. All patients with no flow (8 of 8) showed $\Sigma R/\Sigma ST \leq 2.5$ and all except 1 patient with no flow (7 of 8) showed $\Sigma ST \geq 2.0$ mV. Prediction of preserved flow to the infarct area was possible from the admission electrocardiogram; $\Sigma R/\Sigma ST > 2.5$ —sensitivity 92% (11 of 12), specificity 100%

(8 of 8)—or $\Sigma ST < 2.0$ mV—sensitivity 92% (11 of 12), specificity 88% (7 of 8)—indicated preserved flow. Chronic phase regional wall motion was relatively good in patients with $\Sigma R/\Sigma ST > 2.5$ or $\Sigma ST < 2.0$ mV.

DISCUSSION

The results of this study indicate that the preserved flow to the infarct area can be predicted based on the admission electrocardiogram in the first anterior wall acute myocardial infarction. The regional wall motion during the convalescent period after successful reperfusion also can be predicted from the admission electrocardiogram. Patients with preserved flow showed significantly lower ΣST and higher $\Sigma R/\Sigma ST$ than patients with no flow. An admission electrocardiographic finding of $\Sigma R/\Sigma ST > 2.5$ or $\Sigma ST < 2.0$ mV indicates preserved flow to the infarct area and relatively good regional wall motion in the chronic stage after successful reperfusion.

Generally, the effect of reperfusion is greatest in patients treated earliest. Preservation of left ventricular function often occurred when reperfused within 4 hours.¹⁻³ The time that elapsed between the onset of chest pain and the development of Q waves on the electrocardiogram was variable. This variability is usually attributed to the difference in the development of collateral vessels and the preserved anterograde flow of the

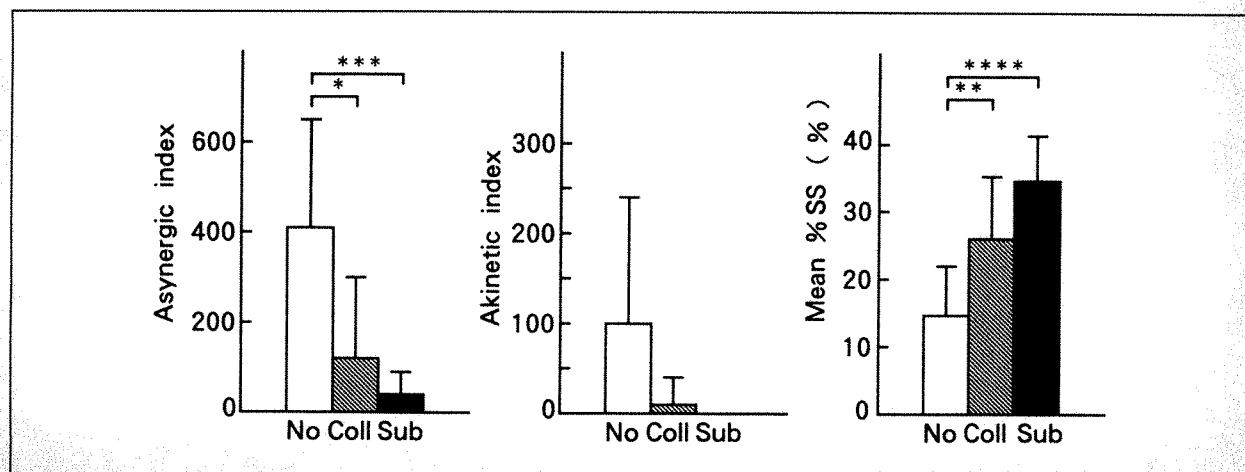


FIGURE 3. Relation between regional wall motion during the convalescent period and coronary arteriographic findings in the acute stage. Coll = intact collateral group; No = no-flow group; Sub = subtotal obstruction group; %SS = percentage systolic shortening. * $p < 0.05$; ** $p < 0.02$; *** $p < 0.005$; **** $p < 0.001$.

infarct-related artery.⁶⁻⁸ Rentrop et al⁸ reported that the critical time interval for preservation of left ventricular function in patients with well-developed collaterals may be >6 hours. Preserved flow to the infarct area has a protective effect on myocardial cell necrosis.^{4,9}

ST-segment elevation has been used as an indicator of "ischemic injury".^{10,11} In experimental animals, the degree of ST-segment elevation after coronary occlusion was correlated with regional blood flow, especially subepicardial blood flow and subsequent myocardial necrosis.¹²⁻¹⁴ Reduction of R-wave amplitude is thought to reflect the loss of viable myocardium, a mixture of viable and necrotic myocardium.¹⁵

Recently, Cohen et al¹⁶ reported that patients with adequate collateral flow had only minimal ST-segment elevation during transient coronary occlusion compared with patients without collaterals who showed severe ST-segment elevation. Hackett et al¹⁷ reported that spontaneous coronary recanalization and reocclusion frequently occur in the early phase of myocardial infarction. They noted that marked ST-segment elevation was associated with total coronary occlusion and partial resolution of ST-segment elevation with coronary patency but with poor runoff.

Prediction of preserved flow to the infarct area from the admission electrocardiogram before initiation of re-

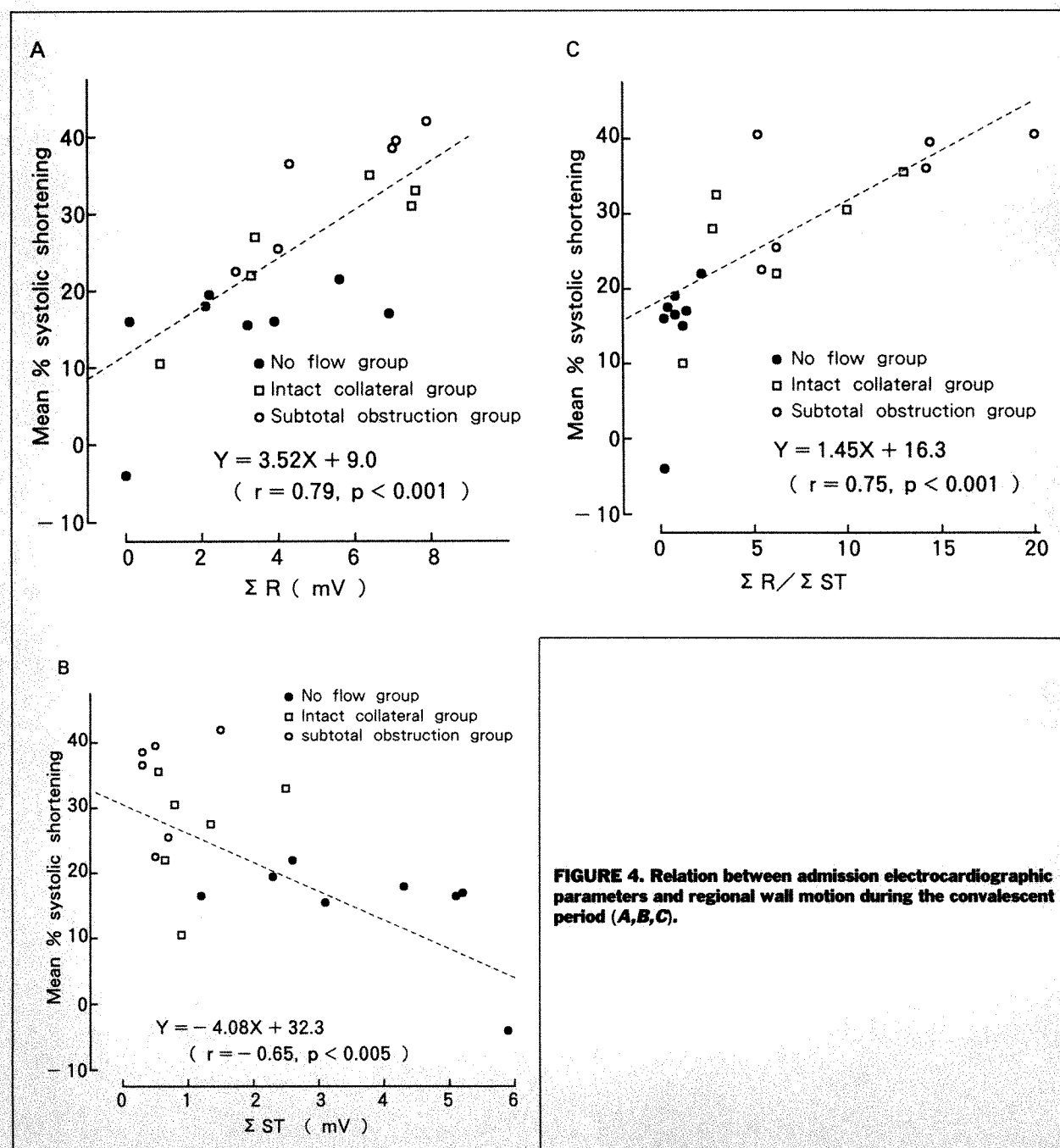


FIGURE 4. Relation between admission electrocardiographic parameters and regional wall motion during the convalescent period (A,B,C).

perfusion therapy is thought to be important. But the value of the admission electrocardiogram in detecting preserved flow is not entirely clear.¹⁸ Our results showed that prediction of preserved flow was possible by using $\Sigma R/\Sigma ST > 2.5$ or $\Sigma ST < 2.0$ mV. ST-segment elevation alone may be a simpler determination. But the magnitude of ST-segment elevation diminishes with the lapse of time and R-wave amplitude also diminishes.^{19,20} It is probable that ST-segment elevation alone cannot correctly differentiate preserved flow from no flow if the duration of symptoms is long. And chronic phase regional wall motion was correlated better with $\Sigma R/\Sigma ST$ than ΣST alone. Thus, it is preferable to use not only ST-segment elevation alone but also R-wave amplitude in conjunction with ST-segment elevation.

Several limitations must be considered in interpreting our results. First, the ST-segment elevation was influenced by various conditions, including electrolytes, conduction disturbance and sympathetic stimulation.¹⁰ In our study, no patients had electrolyte imbalance. Heart rate on admission and the prior incidence of hypertension were not different among the 3 groups. Patients with conduction disturbances were excluded. So it appeared that ST-segment elevation could be used for evaluation. Second, it is not possible to relate regional wall motion in the chronic stage directly to the reperfusion therapy, since spontaneous improvement of left ventricular function occurs in patients with subtotal obstruction whether there is intervention or not.²¹ Third, preserved flow to the infarct area and chronic phase regional wall motion could be predicted from the admission electrocardiogram in a small group of select patients presenting with their first anterior wall acute myocardial infarction, but these results cannot necessarily be applied to other sites of infarction.

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Reocclusion Three Months After Successful Thrombolytic Treatment of Acute Myocardial Infarction with Anisoylated Plasminogen Streptokinase Activating Complex

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Thirty consecutive patients with acute myocardial infarction (AMI) were treated with anisoylated plasminogen streptokinase activating complex (APSAC) within 4 hours after onset of symptoms. After 1.5 and 48 hours, patency of the infarct-related vessel and the quantitative degree of residual diameter stenosis were studied by selective coronary angiography. Ventriculograms were made to determine the global left ventricular ejection fraction. Patients showing patency at 48 hours were reevaluated angiographically after 3 months. At 1.5 and 48 hours after APSAC administration patent vessels were demonstrated in 65 and 69% of patients, respectively. Mean residual stenosis decreased significantly from $56 \pm 11\%$ at 1.5 hours to $46 \pm 13\%$ at 48 hours ($p < 0.01$). Patients not responding to thrombolytic therapy showed significant deterioration of the left ventricular function during the first 48 hours after AMI. Side effects were minor and mainly associated with invasive procedures. Despite adequate oral anticoagulation, angiographically documented reocclusion at 3 months amounted to 28%. Reocclusion, however, was neither associated with clinically documented reinfarction, nor with a decrease in the left ventricular ejection fraction. Our study shows that APSAC is an effective thrombolytic agent in AMI but that late reocclusion may occur. Oral anticoagulants appear to be less effective in the prevention of reocclusion in the treatment regimen after thrombolysis.

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Coronary thrombosis is the commonly accepted cause of acute myocardial infarction (AMI).¹ Intravenous thrombolytic treatment with streptokinase is well established as effective therapy for improving survival^{2,3} and preserving left ventricular function.^{4,5} During the last decade, new intravenous thrombolytic drugs such as recombinant tissue-type plasminogen activator and anisoylated plasminogen streptokinase activating complex (APSAC) have emerged. Each of these drugs is effective.^{6,7} Only APSAC can be given as a slow bolus injection. Because of its long plasma half-life, APSAC exhibits prolonged action, a property that has been related to a low incidence of early reocclusion.⁸ However, little is known about reocclusion in the subsequent period. We therefore studied the 3-month reocclusion rate in patients with AMI treated with APSAC.

METHODS

Patients: Patients who were 70 years or younger were eligible if they had the onset of symptoms suggestive of AMI within the previous 4 hours. In addition, electrocardiographic ST-segment elevation of at least 0.1 mV in ≥ 1 of the standard leads or at least 0.2 mV in ≥ 2 of the precordial leads in a 12-lead registration was required. Symptoms had to be unresponsive to sublingual glyceryl trinitrate. Patients were excluded if contraindications for thrombolytic treatment were present.

Study protocol: Treatment was started with nitroglycerin and lignocaine infusion followed by a bolus injection of 100 mg prednisolone. Subsequently, 30 U of APSAC (Eminase®-Beecham) was given intravenously in 4 to 5 minutes. Intravenous therapy with heparin was supplied 4 to 6 hours after APSAC in a dosage of 30,000 IU in 24 hours and was continued until an adequate level of anticoagulation had been achieved with acenocoumarol, which was started after 48 to 72 hours. Oral anticoagulation was continued for at least 3 months. Antiplatelet therapy was not part of the treatment regimen. Heart catheterization by means of the Judkins technique was performed 1.5 (range 1 to 3) and 48 hours (range 36 to 60) after the administration of APSAC in all patients. Patency and percentage of residual diameter stenosis of the infarct-related vessel were assessed by coronary angiography. Patency was documented according to the score used in the Thrombolysis in Myocardial Infarction Study.⁶ Patients with grade 0 or 1 perfusion were classified as occluded, those

TABLE I Patency Rates in the Course of Three Months

Coronary Artery	No.	Time of Angiography		
		1.5 hrs	48 hrs	3 mos
Left anterior descending	14	8/11	11/14	6/10
Right coronary	11	6/11	6/11	4/5
Left circumflex	4	3/4	3/4	3/3
Patency (%)		17/26* (65)	20/29 (69)	13/18† (72)

* No angiography was obtained from 3 living patients for logistic reasons; 1 patient died <1.5 hours.

† Only patients with a patent infarct-related vessel at 48 hours were examined 3 months after treatment; 1 patient underwent coronary artery bypass surgery and 1 patient died <3 months.

with grades 2 and 3 as patent. Quantification of coronary residual stenosis was realized using the computer-assisted cardiovascular angiography analysis system.^{9,10} Global left ventricular ejection fraction was assessed by quantitative analysis of the left ventricular angiograms in the right anterior oblique projection. In patients with a patent vessel at 48 hours, heart catheterization was repeated at 3 months. Twelve-lead electrocardiograms were made and blood samples were collected for creatine kinase level determination before treatment and serially after the administration of APSAC.

Statistical analysis: Results for continuous variables are presented as mean $\pm$ standard deviation. The Student unpaired *t* test was used to assess differences between patients with patent and nonpatent vessels. Comparisons within each group were made with the paired Student *t* test. A *p* value <0.05 was considered significant.

RESULTS

Thirty consecutive patients (23 men, 7 women) ranging in age from 33 to 70 years (mean 55) with AMI (15 anterior, 15 inferior) participated in the study. The mean overall delay between onset of symptoms and thrombolytic treatment was 2.6 ± 0.9 hours. One patient died in cardiogenic shock within 1.5 hours after treatment with APSAC. Three patients were not subjected to angiography at 1.5 hours for logistic reasons. Seventeen infarct-related coronary vessels in 26 patients at 1.5 hours were patent (65%). Forty-eight hours after the administration of APSAC, patency was found in 20 of 29 patients (69%), including the aforementioned 3 patients (Table I). No reocclusion occurred between 1.5 and 48 hours. There was no significant relation between outcome of thrombolytic therapy and duration of symptoms. One patient, with a patent right coronary artery, underwent emergency bypass surgery soon after the coronary angiography at 48 hours because of symptoms of anterior myocardial ischemia. Another patient with a patent left anterior descending artery at 48 hours died suddenly at home within 3 months. Two patients with a nonpatent infarct-related vessel died between the second day and the end of the 3-month follow-up period. They both had cardiac failure.

Angiography after 3 months was repeated in 18 patients who had a patent vessel after 48 hours. The patient who underwent bypass surgery was excluded. Patency was demonstrated in 13 (72%). Reocclusion was

TABLE II Global Left Ventricular Ejection Fraction (%)

Time	Result of Coronary Angiography		<i>p</i> Value*
	Patent	Occluded	
1.5 hours	67 $\pm$ 14	49 $\pm$ 22	<0.05
48 hours	59 $\pm$ 16	41 $\pm$ 20†	<0.02
3 months	62 $\pm$ 15		

* Between-group comparisons; † *p* <0.01 vs baseline.

found in 5 patients (1 right coronary artery, 4 left anterior descending coronary artery). In none of these 5 patients did a documented reinfarction occur.

The mean percentage diameter stenosis in patent infarct-related arteries decreased significantly between 1.5 and 48 hours from 56 ± 11 to $46 \pm 13\%$ (*p* <0.01). No further significant improvement was found after 3 months when $40 \pm 14\%$ residual coronary diameter stenosis was demonstrated in the 13 patent vessels.

Left ventricular ejection fraction differed significantly between patients with a patent and a nonpatent vessel at 1.5 hours (67 ± 14 and $49 \pm 22\%$, *p* <0.05) and 48 hours (59 ± 16 and $41 \pm 20\%$, *p* <0.02) after treatment with APSAC. Patients with an occluded vessel also showed a significant decrease between 1.5 and 48 hours after treatment (Table II). These patients with an occluded vessel were not reassessed at 3 months. No significant decrease of the left ventricular ejection fraction was found in 5 patients demonstrating reocclusion at 3 months; values at 48 hours and 3 months were 53 ± 14 and $57 \pm 14\%$, respectively.

Neither creatine kinase levels nor creatine kinase-MB levels were significantly different in patients with a patent or an occluded vessel. However, the time to peak level of each was significantly shorter in patients with a patent vessel.

Mild bleeding, mainly at puncture sites, occurred in 9 patients. Two patients received a blood transfusion for moderate bleeding. A purpuric rash developed in 1 patient on the fifth day after treatment. A skin biopsy showed this to be due to a nonspecific vasculitis.

DISCUSSION

In our study 3 patients did not undergo angiography at 1.5 hours. However, these patients showed rapid relief of chest pain, quick improvement of electrocardiographic repolarization changes and an early peak of creatine kinase-MB. These findings have been shown to be strongly predictive for patency of an infarct-related vessel.¹¹ Therefore, it seems likely that in case of angiography of all patients, the patency results at 1.5 and 48 hours after APSAC would have been similar. Forty-eight hours after treatment with APSAC 69% of the patients in our study had a patent infarct-related vessel. This figure corresponds to the 60 to 70% of thrombolytic success reported in a review by Marder and Sherry.⁸ These investigators estimated the incidence of reocclusion after treatment with APSAC to be 10%. However, this low percentage was derived from a limited number of patients in whom angiography was repeated 24 hours after treatment.^{12,13} We found no reocclusion between

1.5 and 48 hours. A similar result was obtained in a study of 99 patients with AMI also treated with APSAC. In these patients angiography was performed at 1.5 and 24 hours after treatment.¹⁴ The low rate of early reocclusion after treatment with APSAC is probably due to a long-lasting extensive fibrinogenolysis. In such a hypocoagulable state a more complete lysis of the residual thrombus can be elicited, as was also demonstrated in our study. Thorough lysis was one of the factors postulated to be preventive for reocclusion.¹⁵

Only 1 study reported reocclusion data 4 weeks after therapy with APSAC.¹⁶ These investigators found reocclusion in 5 of 37 (14%) of the infarct-related vessels. However, data of some of the patients were lacking, which may partly explain the low percentage. In our study angiographic reocclusion at 3 months was found in 5 of 18 patients (28%). This relatively high rate, despite adequate oral anticoagulation, is disappointing. Recently it was shown in animal experiments that platelets have a vital role in reocclusion after thrombolysis.¹⁷ Thus, instead of oral anticoagulants, platelet inhibitors might have been a more appropriate approach to prevent reocclusion. Since the Second International Study of Infarct Survival, the issue of aspirin in the treatment of AMI is also acknowledged.³

It should be emphasized that none of the patients with reocclusion at 3 months had documented reinfarction or decrease of the left ventricular ejection fraction. Obviously, reocclusion after initial successful therapy with APSAC appears not to be as deleterious as complete treatment failure. This could be explained by the restriction of the cardiac area at risk in the acute phase through reperfusion and subsequent adaptation of the ventricle by collateral blood supply.

The significant decrease in coronary residual diameter stenosis in the first 48 hours after successful treatment corresponds with the findings in studies with streptokinase¹⁸ or recombinant tissue-type plasminogen activator.¹⁹ Their thrombolytic effect persists for a longer period than might be expected from their plasma half-life.

Thrombolytic therapy of AMI with APSAC has been shown to preserve the left ventricular ejection fraction compared to conventional heparin therapy.²⁰ In our study this only occurred in patients responding to APSAC, whereas a significant decrease of the left ventricular function during the first 48 hours was seen in patients resistant to thrombolytic treatment. Thus, it appears highly desirable to achieve reperfusion of an occluded coronary vessel in the acute phase of AMI to improve myocardial function.

Bleeding complications were infrequent and considered not serious in most patients. One case of vasculitis, which resolved quickly and spontaneously, was seen. Vasculitis results from APSAC's antigenic properties and has been described earlier in a limited number of patients.²¹

In this study APSAC proved to be effective and safe. Early reocclusion was absent but reocclusion after 3 months was found in 28% of the patients. Failure to achieve patency, however, was more deleterious than failure to maintain patency. To avoid reocclusion, therapy

with aspirin might be more appropriate instead of oral anticoagulants. This should be confirmed in a controlled trial in patients with AMI after thrombolytic therapy.

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Influence of Heparin Therapy on Percutaneous Transluminal Coronary Angioplasty Outcome in Unstable Angina Pectoris

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The acute procedural outcome of percutaneous transluminal coronary angioplasty in 304 patients with unstable angina was retrospectively examined with respect to the influence of prolonged preprocedural intravenous heparin therapy. Clinical and angiographic success in 135 patients receiving heparin therapy for ≥ 24 hours was 91% while such success was noted in 81% of patients not treated with heparin ($p = 0.02$). The incidence of immediate postprocedural thrombotic vessel occlusion was higher in the nonheparin group than in the heparin-treated group (8.3 vs 1.5%, respectively, $p < 0.01$). In addition, the overall rate of thromboembolic target and branch or distal vessel occlusion was 12.4% in the nonheparin group and 1.5% in the heparin-treated group ($p < 0.001$). Thus, prolonged preprocedural intravenous heparin administration in this well-defined group of patients with unstable angina resulted in an improved procedural success rate and a significant decrease in the risk of abrupt vessel closure. These observations are concordant with current understanding of the pathophysiology of unstable angina.

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The role of percutaneous transluminal coronary angioplasty (PTCA) in the treatment of medically unresponsive stable angina is well established. As a result of these dramatic effects on clinical outcome, the role of PTCA as applied to patients with unstable ischemic syndromes continues to evolve.¹⁻⁶ Early reports from the National Heart, Lung, and Blood Institute (NHLBI) Registry noted an increased risk of acute complications during PTCA in patients with unstable angina.⁷ More recent studies continue to note a higher incidence of acute procedural complications in patients with unstable angina.^{3,4,8} The significance of periprocedural coronary artery occlusion is emphasized by the substantial increase in frequency of adverse clinical sequelae.⁹

The pathophysiology of unstable ischemic syndromes is recognized to be dynamic and, in large part, thrombotic.¹⁰ Therefore, thromboembolic complications of PTCA in this clinical setting would not be unexpected. It is notable that a follow-up report from the NHLBI identified, among other variables, coronary thrombus as a risk factor for an unsuccessful procedural outcome.¹¹ This increased understanding of the pathologic basis of unstable ischemic syndromes coupled with a continued concern over thrombotic procedural complications led us to retrospectively examine our experience with preprocedural systemic anticoagulation in patients with unstable angina undergoing PTCA.

METHODS

Clinical and angiographic records of 764 consecutive patients referred for PTCA from January 1985 through May 1987 were reviewed. Patients with evolving myocardial infarction and patients undergoing PTCA within 24 hours of thrombolytic therapy for acute infarction were excluded from analysis. In particular, attention was directed to the presence of unstable angina, defined as follows: rest angina unresponsive to standard medical therapy, including parenteral nitroglycerin; and electrocardiographic evidence of reversible myocardial ischemia without infarction, i.e., ST-segment deviation and/or symmetric T-wave changes. Hospital records were reviewed for demographic data, clinical outcome, in-hospital management and concomitant medication, including the duration and adequacy of intravenous heparin. The adequacy of intravenous heparin administration was verifiable in 80% of these patients. Documented prolongation of the partial thromboplastin time

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TABLE I Clinical Characteristics

	Heparin (%)	No Heparin (%)
M/F	98/37	115/54
Mean age (yrs)	66 ± 25	60 ± 19
Systemic hypertension (>150/90)	64 (48)	84 (50)
Obesity	25 (19)	35 (21)
Cigarette smoking	54 (40)	80 (47)
Congestive heart failure	13 (10)	27 (16)
Diabetes mellitus	20 (15)	29 (17)
Recent AMI	40 (30)	57 (34)
Prior CABG	16 (12)	25 (15)
Prior thrombolytic therapy	14 (10)	3 (1.7)
Aspirin therapy	122 (89)	138 (82)

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting.

to $>1.5 \times$ control was required for patient inclusion in the heparin-treated group. In addition, documentation of a prolonged partial thromboplastin time within 24 hours of the PTCA was also required. Angiographic review was performed by 2 experienced observers blinded with respect to pretreatment, clinical presentation or clinical outcome. Successful PTCA outcome was defined as a post-PTCA stenosis of the target vessel of $<50\%$ without procedural death, infarction, or coronary bypass surgery. Coronary thrombus was defined as previously reported.¹² All PTCA procedures were performed by the same group of staff angiographers over the time interval of the study. All studies were performed with a movable guidewire system and ionic contrast media. Finally, the adequacy of intraprocedural anticoagulation with heparin was monitored by assessment of the activated clotting time. Periodic monitoring of the activated clotting time was performed throughout the procedure and additional bolus heparin was administered for values <300 seconds. After PTCA, all patients were routinely observed in the cardiac catheterization laboratory for ≥ 30 minutes. Therefore, it should be emphasized that the outcome of the procedure reflects this time interval.

Univariate comparison of categorical variables was performed using chi-square analysis or Fisher's exact test, where appropriate. A p value <0.05 was considered statistically significant.

RESULTS

During the time interval of this analysis, 764 patients underwent PTCA. Twenty-nine patients were referred for PTCA with an acute myocardial infarction, 431 patients had stable or progressive angina pectoris and 304 patients had unstable angina (defined previously). Of the latter group, 135 patients received continuous intravenous heparin for ≥ 24 hours before PTCA while 169 patients received either no heparin ($n = 162$) or an infusion for <24 hours ($n = 7$). For simplicity, we grouped these patients together as a no-heparin population. Importantly, this distribution did not change between the first 15 months of this review and the last 14 months. Table I lists the clinical characteristics of these 2 groups. No significant intergroup differences were present with respect to age, sex distribution, frequency

TABLE II Angiographic Characteristics

	Heparin (%)	No Heparin (%)
Coronary artery dilated		
LAD	57 (41)	92 (50)
LC	31 (22)	33 (18)
Right	44 (32)	46 (25)
SV graft	7 (5)	13 (7)
Total occlusion	11 (8)	18 (10)
Multivessel disease	12 (19)	19 (11)
Intracoronary thrombus	25 (19)	17 (10)
Complex anatomy	14 (10)	12 (7)

LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; SV = saphenous vein.

of systemic hypertension, obesity, smoking history, congestive heart failure, insulin-requiring diabetes, recent myocardial infarction (>24 hours but <2 weeks) or preexistent aspirin therapy (given ≥ 1 day before PTCA with a majority of each group receiving aspirin on a chronic basis).

Table II lists the angiographic characteristics of the 2 groups. There was no difference in the distribution of the culprit vessel nor was there a difference in the frequency of complete occlusion of the target artery. The difference in the incidence of coronary thrombus in the target artery was not statistically significant. Multivessel disease ($>50\%$ diameter decrease) was equally distributed. The incidence of "complex" anatomy (lesion length >1 centimeter, juxtabifurcation lesion, severe angulation or tandem lesions) was also comparable. It should be noted that in the 135 patients in the heparin-treated group, PTCA was attempted in 139 vessels, while in the nonheparin group of 169 patients, PTCA was attempted in 184 vessels. In all instances, PTCA of the target vessel was attempted before approaching the secondary lesions. Over the time interval of the study, it was the prevailing philosophy of the catheterization laboratory staff not to attempt complete revascularization during the same procedure. Thus, procedural success is expressed on a per patient basis.

There was a trend toward a longer time interval from hospital admission (the result of an intensification of symptoms) to diagnostic catheterization in the heparin group (heparin, 5.6 ± 4.5 days; no heparin, 3.4 ± 3.6 days), although this difference was not statistically significant. The time interval from diagnostic angiography to PTCA was similar between groups (heparin, 3.5 ± 2.5 days; nonheparin, 2.7 ± 2.0 days). It is important to note that many patients were referred for diagnostic catheterization and/or PTCA from other institutions. Thus, the timing of angiography as well as the institution of heparin therapy were frequently decided by referring physicians. However, within our institution, the indications for PTCA in this population were uniform, i.e., unstable angina refractory to an intensive medical regimen.

The overall success rate of PTCA for the entire population of 304 patients with unstable angina was 86%. Acute procedural complications resulting in unresolved vessel occlusion and emergent coronary bypass surgery

occurred in 4% of patients. The overall frequency of procedural-related myocardial infarction was 2.3%. There was 1 procedural-related mortality (0.3%). Over the same time interval of this review, the success rate for PTCA in patients without unstable angina was 91% with a 1% incidence of urgent bypass surgery, 0.6% incidence of myocardial infarction and no procedural-related deaths. Univariate analysis of the demographic, clinical and angiographic features listed in Tables I and II in those 44 patients with an unsuccessful PTCA and the 260 patients with a successful PTCA failed to reveal any statistically significant differences. Only the presence of heparin therapy (52% in the success group, 27% in the failed group, $p < 0.01$) was significantly different. The incidence of complex anatomic features was not significantly different (12% in the successful PTCA group, 17% in the failed group), although the small sample size of failed procedures may obscure any true difference.

Procedural success was noted in 123 of the 135 patients receiving heparin therapy for ≥ 24 hours (mean 5.7 days, range 2 to 9) before PTCA while such success was noted in 137 of the 169 patients not receiving heparin (Figure 1). This difference, 91 versus 81% respectively, was statistically significant ($p = 0.02$). As also shown in Figure 1, procedural failure and vessel occlusion were higher in the nonheparin group. Procedural failure due to the inability to cross the target lesion with a guidewire or balloon catheter (no cross) was significantly more common in the nonheparin group. However, the frequency of total target vessel occlusion was similar in the 2 groups (Table II). While angiographically evident coronary artery dissection leading to unresolved vessel closure was equally prevalent in the 2 groups, unresolved closure in the absence of an angiographically evident dissection was significantly more common in the nonheparin group (8.3 vs 1.5%, $p =$

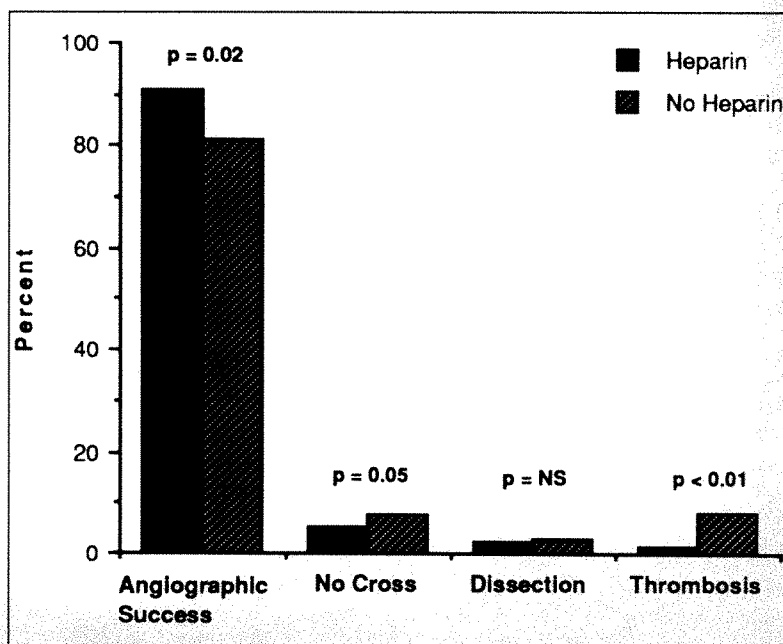
0.009). The administration of intracoronary nitroglycerin failed to establish reperfusion and, thus, coronary vasospasm was not contributory. Finally, in all cases, angiographic evidence of thrombus formation and propagation was noted. Of note also was a greater frequency of nondissection-related side branch occlusion and distal embolization and occlusion in the nonheparin group (4 vs 0%, $p = 0.1$). Thus, the overall rate of thromboembolic vessel occlusion (both target and branch or distal vessel) was 12.4% in the nonheparin group and 1.5% in the heparin-treated group ($p < 0.001$). Notably, the 2 patients with thrombotic vessel occlusion in the heparin group and 12 of the 14 patients with thrombotic occlusion in the nonheparin group were receiving aspirin therapy. Three patients (2.2%) in the heparin group required emergent surgical revascularization for ischemic symptoms and unresolved vessel closure while 10 patients (5.9%) in the nonheparin group required urgent surgical intervention ($p = 0.1$). Electrocardiographic evidence of myocardial infarction was noted in 2 patients in the heparin group and 5 patients in the nonheparin group (difference not significant). Finally, intracoronary streptokinase infusion in vessels with thrombotic occlusion was used in 5 patients in the heparin group (with successful reperfusion in 4) and in 4 patients in the nonheparin group (with successful reperfusion in 3).

Importantly, there were no reports of premature discontinuation of the heparin infusion as a result of bleeding nor were there any significant differences in the incidence of invasively related bleeding complications or transfusion requirements.

DISCUSSION

It is now appreciated that in contrast to the underlying pathophysiology of clinically stable coronary artery disease, unstable angina represents a dynamic spectrum of events, including plaque disruption, platelet aggrega-

FIGURE 1. Procedural success was noted in 91% of heparin-treated group and 81% of nonheparin group. Statistically significant increases in procedural failure as the result of inability to cross target lesion (heparin 5.2%, no heparin 7.7%) as well as immediate postprocedural thrombotic vessel occlusion (heparin 1.5%, no heparin 8.3%) were noted in nonheparin group. NS = not significant.



tion and occlusive thrombus formation.^{10,13,14} The central role of intracoronary thrombosis in unstable angina coupled with the recognition that the angiographic presence of thrombus is a predictor for an adverse in-hospital outcome¹⁵ has led to alterations in the treatment program for these patients. Systemic anticoagulation with heparin,¹⁶ administration of antiplatelet agents^{16,17,18} and thrombolytic therapy^{19,20} have all been reported to have a beneficial effect on clinical outcome. More aggressive approaches to the treatment of patients with unstable angina must then account for not only this inherent tendency for vessel thrombosis but also the thrombogenic sequelae of PTCA. Many of the features of successful balloon angioplasty, i.e., plaque fissuring, intimal disruption and platelet aggregation, resemble the histopathologic changes seen in the coronary circulation of patients with unstable angina.^{13,14}

Our analysis noted an improved clinical and angiographic outcome of PTCA in those patients with unstable angina receiving prolonged intravenous heparin before PTCA. The higher procedural failure rate in the nonheparin group reflects the thrombogenic features of this syndrome. The frequency of thrombotic vessel occlusion was 5-fold greater in patients not treated with heparin and the overall frequency of thromboembolic occlusive events was 8-fold greater in this group. The increased frequency of emergent surgical revascularization, albeit not statistically significant, in the nonheparin group also reflects the increased incidence of thrombotic vessel occlusion. Patients may require emergency surgical intervention for vessel occlusion secondary to occlusive dissection or thrombus formation. In this series, the majority of occlusive events leading to urgent surgery was primarily thrombotic in origin. The fraction of patients receiving adequate aspirin therapy was similar in the 2 groups. Thus, the improved outcome in the heparin-treated group underscores the importance of chronic inhibition of thrombin activity. Effects of heparin on myointimal proliferation²¹ and thrombus propagation²² are additional possible explanations for our observations.

The nature of this retrospective study presents certain limitations to the acceptance of our conclusions. However, the size and relative uniformity of this rigorously defined clinical population as well as the time interval over which the data were gathered provide additional support for our conclusions. Many variables have been shown to affect the acute procedural outcome of PTCA.²³ In our study, univariate analysis failed to identify differences in the frequency of those preprocedural clinical and angiographic variables previously shown to affect outcome. Only the presence of heparin therapy was significantly different between the successful PTCA group and the failed PTCA group. However, the small number of angiographically related risk factors in each group may result in a β error. Importantly, the distribution of patients receiving heparin was not significantly changed over the time of the study. At present, however, virtually all patients considered to manifest unstable anginal symptoms receive intravenous heparin therapy and, thus, little opportunity presents itself for a

prospective randomized study. Another concern revolves around the decision for, and timing of, the institution of heparin therapy. Such decisions in our population were made on a case-by-case basis by the patient's attending physician. The decision regarding the timing of the PTCA was made by the attending physician as the clinical situation demanded. All PTCA procedures were performed in a standardized fashion by 4 experienced interventional angiographers. Although a variable delay was present between the time of hospital admission (an index of the onset of medically unresponsive symptoms) and PTCA, the mean interval was not significantly different between groups. It is recognized that the duration of symptoms before PTCA may also be an important variable affecting outcome.²⁴

The frequency of identifiable coronary thrombus in our study is in agreement with some reports,^{15,25,26} but significantly lower than others.^{27,28} It is recognized that the time from the onset of symptoms to angiography significantly influences the angiographic recognition of thrombus.²⁷ This variable was uncontrolled in our study and may account for the disparity, albeit not significant, in frequency of coronary thrombus between groups. All patients underwent diagnostic angiography within 7 days of their hospitalization. This difference in frequency of recognizable thrombus between groups, as well as the discrepancy with other reports noting a higher incidence of coronary thrombus in patients with unstable angina, does not minimize the importance of our findings. In fact, the beneficial effects of heparin were apparent in spite of a higher incidence of angiographically recognized coronary thrombus and a higher incidence of patients who recently received thrombolytic therapy for evolving myocardial infarction. The angiographic presence of thrombus is itself a risk factor for an adverse procedural outcome.¹¹ Moreover, the angiographic identification of coronary thrombus is critically time-dependent²⁷ and coronary thrombus has been demonstrated by angiography in patients without angiographic evidence of clot.²⁹ Nevertheless, in spite of the likely underestimation of the frequency of coronary thrombus in our study population, our conclusions apply in a large group of patients with unstable angina, irrespective of the angiographic presence of thrombus at the time of diagnostic catheterization.

Finally, while it is recognized that virtually all PTCA procedures result in variable degrees of intimal disruption, we emphasize that we considered vascular occlusion to be the result of coronary arterial dissection only when the immediate postprocedural angiogram revealed the characteristic features of dissection.⁸ Similarly, vascular occlusion due to thrombosis was, by definition, present when there was no angiographically evident dissection. Clearly, these 2 complications may coexist in many patients. In all instances, however, there was interobserver agreement with respect to the originating event.

The central finding of our study was that a significant increase in PTCA success rate in patients with unstable angina was noted in the group of patients receiving continuous intravenous heparin for >24 hours.

These findings need to be taken into account in the interpretation of studies of the safety and efficacy of aggressive treatment programs for patients with unstable angina.

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Transluminal Atherectomy of Saphenous Vein Aortocoronary Bypass Grafts

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Angioplasty of stenotic saphenous vein aortocoronary bypass grafts is often unsatisfactory because of the relatively high incidence of acute complications and restenosis. During an initial evaluation of transluminal coronary atherectomy, 14 patients had atherectomy of saphenous vein graft lesions (15 grafts). Atherectomy was successful in 13 of 14 patients, decreasing the mean diameter of stenosis from 85 to 15%. In 1 patient, the lesion could not be crossed by the atherectomy device. The following 3 minor complications occurred: 1 embolus of atheromatous material; 1 air embolism; and 1 transient thrombosis leading to subendocardial myocardial infarction. Of the 14 patients, 8 underwent angiography 4 to 6 months after atherectomy; 5 patients had restenosis and 3 had widely patent grafts. Four other patients were clinically evaluated at 3 months after atherectomy. Two were asymptomatic, 1 had class II angina and 1 had class III angina. Transluminal atherectomy achieved excellent immediate results with a low incidence of major complications in the treatment of stenosed saphenous vein bypass grafts. However, preliminary follow-up results suggest a high incidence of restenosis.

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Balloon angioplasty of stenosed saphenous vein grafts is a well-accepted treatment; its success is limited by the risk of acute complications and high restenosis rates.¹⁻⁷ Directional atherectomy, which removes atheromatous tissue, has been recently introduced.⁸⁻¹¹ It has been shown to be safe and effective when applied in native coronary arteries.¹² It has been proposed that atherectomy might decrease restenosis rates by creating a smooth luminal surface and optimal flow conditions with minimal injury to the vessel wall.¹³ It also might decrease initial complications in native coronary arteries. These advantages could be very helpful when applied to the treatment of saphenous vein bypass grafts. This report describes the initial results and preliminary follow-up of transluminal atherectomy applied to aortocoronary venous bypass grafts.

METHODS

Patient group: Between October 6, 1988, and May 16, 1989, 14 patients (12 men and 2 women) were treated for stenosis of saphenous vein grafts with the Simpson directional AtheroCath (Devices for Vascular Intervention). The mean age of the patients was 66 years (range 44 to 83). Selection criteria were the following: a subtotal stenosis(es) of <20 mm in length in a vein graft that was not markedly tortuous and associated limiting angina. Exercise radionuclide ventriculography or tomographic thallium scanning was used to document ischemia when there was any doubt about its presence.

Definitions: Success was defined as a $\geq 40\%$ decrease of the initial stenosis with removal of tissue and no complications requiring operation during the in-hospital follow-up. Transmural myocardial infarction, a vascular complication requiring operation, and death were considered major complications. Others were listed as minor.

Restenosis after atherectomy was defined as a decrease of 30% in the luminal diameter or a loss of $\geq 50\%$ of the initial gain.

Technique and medication: Baseline angiograms were obtained before atherectomy. Patients were pretreated with 325 mg of aspirin and received 15,000 units of heparin intravenously and 0.4 mg of nitroglycerin sublingually at the start of the procedure. An 11Fr introducer sheath was inserted percutaneously into the femoral artery. An 11Fr guiding catheter was then advanced over a dilator and guidewire to the aortic root.

After intubation of the vein graft ostium, the Simpson AtheroCath was introduced into the vein graft over

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TABLE I Clinical Data and Results in 14 Patients Who Had Atherectomy of Saphenous Vein Aortocoronary Bypass Grafts

Case	Age (yr)	Restenotic Narrowing	Bypassed Coronary Artery	Stenosis (%)		Success	Complications	Follow-Up		
				Pre	Post			Duration (months)*	Angiogram	Outcome
1	66	0	Right	90	30	+	0	6	+	Patent
2	68	0	LC	90	0	+	0	5	+	Restenosis—PTCA
3	61	0	LAD	95	0	+	Embolus	6	+	Patent
4	44	0	Right	80	10	+	0	6	+	Patent
5	54	+	LAD	70	20	+	0	4	+	Restenosis—CABG
6	61	0	LC	70	20	+	0	4	+	Restenosis—PTCA
			Right	60	20	+	Thrombus	4	+	Patent
7	77	+	SVG	90	10	+	0	3	+	Restenosis†
8	73	+	SVG	90	35	+	Air embolism	2	+	Restenosis
9	71	0	LAD	80	10	+	0	3	0	No angina
10	57	+	LAD	80	0	+	0	3	0	Angina II
11	83	+	SVG	90	10	+	0	3	0	Angina III
12	66	0	LAD	95	20	+	0	3	0	No angina
13	76	0	LC	95	—	0	Failed PTCA†	Surgery (failed atherectomy)		
14	63	0	LAD	70	30	+	0	<1	0	No angina

* Duration refers to interval from atherectomy to follow-up angiography or, if follow-up angiography was not performed, to interval from atherectomy to August 15, 1989; † patient died.

LAD = left anterior descending artery; LC = left circumflex artery; PTCA = percutaneous transluminal coronary angioplasty; SVG = sequential vein graft to several coronary arteries.

a 0.014-inch guidewire (Figure 1). The device consists of a cylindrical metal capsule with a window opening over 50% of the outer surface. On the opposite side is a balloon that, when inflated to low pressure, pushes the window against the obstructing plaque. A cylindrical cutter, located within the housing, is rotated at a speed of 2,500 rpm over the guidewire by a battery-operated external motor. Once the window has been positioned against the plaque, the motor drive unit is turned on and the cutter is slowly advanced, resecting tissue, which is collected in the distal chamber. This is repeated 4 to 6 times as the window is turned in different positions to cover the entire lesion. The catheter is then withdrawn and the chamber is emptied.

Follow-up: At 3 months, all of the patients had exercise testing and completed a standardized functional questionnaire. All patients with successful atherectomy had another stress test and coronary angiography at 6 months.

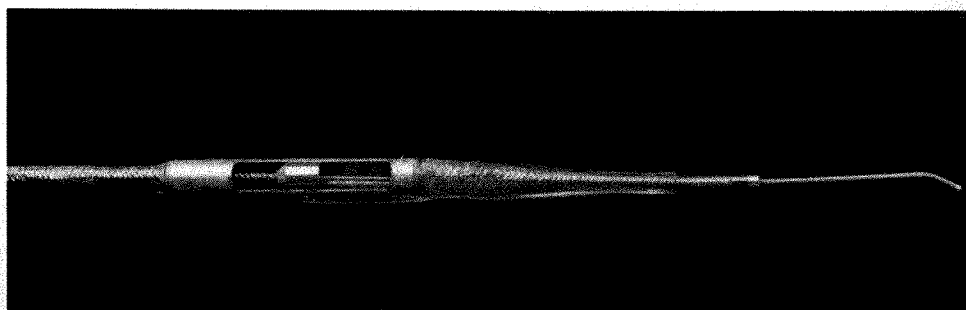
RESULTS

Fourteen patients were treated, 13 in 1 saphenous vein graft and 1 in 2 different grafts. One patient had Canadian Cardiovascular Society class I angina with a markedly positive stress test, 2 had class II, 6 had class III and 5 had class IV angina.

Six grafts were bypasses to the left anterior descending coronary artery, 3 to the right coronary artery and 3 to the left circumflex artery. Three patients had circular sequential grafts to the distal right coronary artery, the obtuse marginal branch artery and the left anterior descending artery. The attempted stenosis was located at the proximal anastomosis in 5 patients and in the body of the vein graft in 9 patients. The mean graft age was 6.4 years (range 2 to 14). Nine patients had primary atheromatous lesions and 5 patients had restenosis after previous percutaneous transluminal coronary angioplasty.

Thirteen (93%) of 14 patients had successful atherectomy (Table I). The mean visually assessed diameter of the stenosis was decreased from 85 to 15%. The mean number of cuts per graft was 12; between 2 and 30 tissue fragments were recovered per graft. In 1 patient with poor left ventricular function, unstable angina, an occluded left anterior descending artery and a severely diseased left circumflex artery, atherectomy was attempted on an eccentric 95% stenosis in the body of a left circumflex vein graft lesion, but the lesion could not be crossed by the guidewire. Conventional angioplasty was then attempted on the native circumflex artery, which was the only patent native vessel, but the procedure resulted in acute occlusion with hemodynamic col-

FIGURE 1. Simpson directional AtheroCath.



lapse. After insertion of an intraaortic balloon pump and full vasoactive support, the patient was sent for emergency surgery but died during induction of anesthesia.

Minor complications occurred in 3 patients. Embolization of atheromatous material led to prolonged pain in 1 patient. This embolus was subsequently removed by the atherectomy catheter without sequelae.

In 1 patient, transient thrombosis with low blood flow occurred after an otherwise successful atherectomy; prolonged angina and mild elevation of creatine kinase ensued, but the patient was asymptomatic thereafter. In a third patient, the balloon ruptured, leading to a small air embolism with prolonged chest pain but no myocardial damage. No vessel wall perforation or dissection was seen.

Table I lists the preliminary results of the follow-up study. Of the 14 patients, 8 (57%) had a follow-up angiogram, 4 at the scheduled 6-month examination and 4 between 2 and 4 months after atherectomy because of recurrence of angina. Of the 4 asymptomatic patients who had angiography at 6 months, 3 had no restenosis (Figure 2) and 1 had restenosis. Among the 4 patients undergoing angiography before 6 months, 4 of 5 grafts had restenosis (Figure 3). Three restenoses occurred in patients treated for postangioplasty restenotic lesions and 2 occurred in patients with primary atheromatous lesions. Grafts with postatherectomy restenosis were slightly older than the others (8.2 vs 6.4 years).

Four other patients had clinical 3-month follow-up only; 2 had no symptoms. One had class II angina but did not have a stress test because of advanced age and debilitation. Another patient had class III angina and an abnormal stress echocardiogram with wall motion changes.

DISCUSSION

Dilation of stenotic saphenous vein grafts is difficult because of the friable consistency of the lesion and vessel and because of the high rates of restenosis (as high as 50%).¹⁻⁷ Our results indicate a high initial success rate with a relatively low incidence of serious complications with atherectomy of saphenous vein bypass grafts. No dissection or intimal flap with subsequent instability was observed; 1 patient had a transient thrombosis with slow blood flow. The only major complication (vascular collapse and death) occurred after balloon angioplasty of a different vessel than the one attempted by atherectomy and cannot be attributed to the atherectomy technique itself. Coronary atherectomy can therefore be applied to older stenosed vein bypass grafts (mean age, 6.4 years) with a degree of safety and quality of initial results comparable to or even better than the results obtained with balloon angioplasty.¹⁻⁷

In vein grafts older than 1 year, the histopathologic characteristics of an occlusive lesion change progressively from fibroproliferative to atherosclerotic.¹⁴ Observations from autopsy and surgical specimens confirm the friable consistency of these lesions, which are at risk of embolization during operation¹⁵ or dilation.^{14,16} In our study, despite the fact that all the grafts treated were ≥ 2 years old, atheromatous embolization occurred only in 1 patient, possibly due to escape from the collection chamber when the cutter was manipulated because the large occlusive filling defect was observed only after multiple manipulations of the device. With more frequent emptying of the chamber and retraction of the cutter only when the window opening is positioned against the vessel wall, no further embolization has been observed.

In some cases, atherectomy may be used for the "rescue" removal of large embolized fragments; the em-

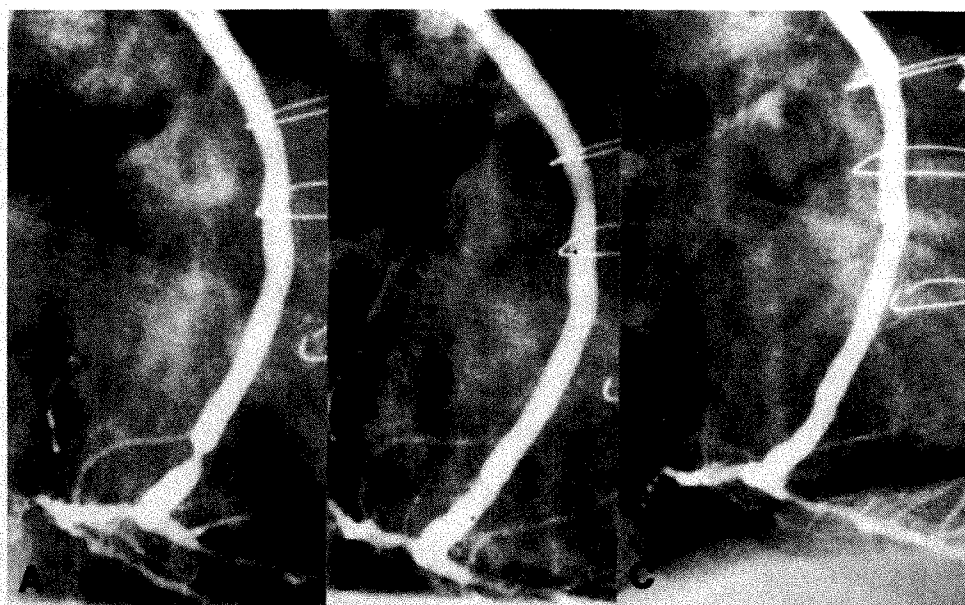


FIGURE 2. Angiograms from case 4 before atherectomy (A), immediately after atherectomy (B) and at 6-month follow-up (C). Atherectomy site is widely patent 6 months after procedure.

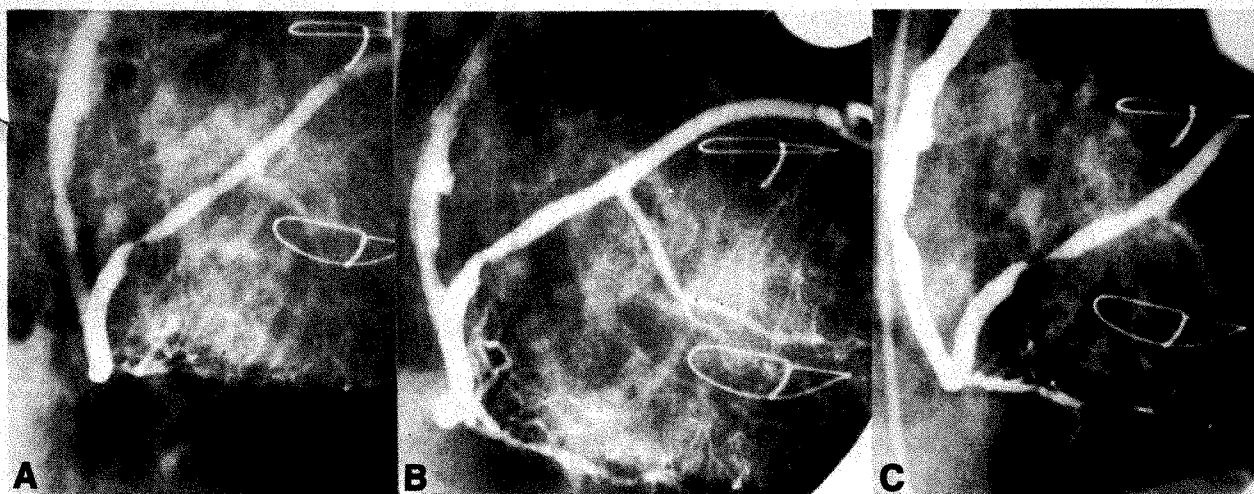


FIGURE 3. Angiograms from case 8 before atherectomy (A), after atherectomy (B) and 2 months after atherectomy (C). A 95% restenotic lesion had developed at atherectomy site.

bolus described in our patient was retrieved by the atherectomy catheter from its distal location, which would not have been possible with a balloon angioplasty catheter.

The limited follow-up information from our study suggests that atherectomy does not solve the issue of restenosis in vein grafts. Among the 8 patients who had angiography during the first 6 months after atherectomy, 5 had a restenosis, 4 of whom were severely symptomatic. These results are similar to those obtained with conventional balloon angioplasty in vein grafts.¹⁻⁷ If confirmed, such data suggest that producing wide lumen patency with improved laminar flow conditions is not enough to prevent restenosis in vein grafts.^{13,17} Histopathologic specimens obtained from 1 patient who later died with restenosis showed a pattern of fibroblastic and smooth muscle cell proliferation very similar to the myointimal proliferation observed after balloon angioplasty.¹⁴ This finding further strengthens the hypothesis that intimal and medial injury and repair are the key mechanisms for restenosis after mechanical injury, regardless of the technique or device applied.¹³ By the time of this observation, 3 of the 5 patients treated for postangioplasty restenotic lesions already had postatherectomy restenosis, suggesting that restenotic lesions in vein grafts are at high risk for further restenosis.

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Long-Acting, Marked Antiischemic Effect Maintained Unattenuated During Long-Term Interval Treatment with Once-Daily Isosorbide-5-Mononitrate in Sustained-Release Form

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In 18 patients with documented coronary artery disease, the antiischemic effect of 50 and 100 mg isosorbide-5-mononitrate (IS-5-MN) in sustained-release (SR) form was investigated using a randomized, double-blind, crossover, placebo-controlled protocol. After the initial administration of both dosages, compared to placebo there were significant reductions in exercise-induced ST-segment depression and significant increases in ischemia-free exercise time at all times of testing. At 12 hours, the 100-mg dosage still amounted to >50% of its maximum and was significantly more marked than the 50 mg dose. Accordingly, the 100-mg dosage can be assumed to confer a longer duration of action. At the end of 3 weeks of long-term treatment, the significant antiischemic effects were not diminished versus those observed after initial administration. There was no evidence of tolerance development with either dosage. The IS-5-MN plasma concentration during long-term administration displayed, within the 24-hour treatment cycle, a clear decrease to low baseline values and a marked 5- to 7-fold increase after the daily dose in accordance with the response known to be prerequisite to successful interval treatment. Thus, the once-daily administration of IS-5-MN SR with dosages of 50 mg and, more markedly, 100 mg, provides effective antiischemic protection throughout the daily period of most physical activities in patients with stable angina pectoris.

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Isosorbide-5-mononitrate (IS-5-MN), a main metabolite of isosorbide dinitrate, was introduced into oral nitrate treatment in 1981, and primarily due to its more predictable pharmacokinetics—a nearly 100% bioavailability as well as an approximately 8-fold longer half-life—it met with rapid acceptance.¹ To facilitate patient compliance through once-daily administration, sustained-release (SR) formulations were developed. While the effectiveness of SR isosorbide dinitrate is well established both for short- and long-term administration,² documentation has not yet been provided for IS-5-MN SR. Accordingly, in a 2-phase controlled study with once-daily regimens of 50 and 100 mg IS-5-MN SR, we investigated the extent and duration of the acute antiischemic action up to 12 hours and compared the effects during long-term treatment to those observed after initial administration to determine if tolerance developed.

METHODS

Patients: The short-term study was carried out in 8 patients, the long-term study in 10 patients. All patients had angiographically documented coronary artery disease with $\geq 75\%$ stenosis of at least 1 major coronary artery and all had reproducible exercise-induced ST-segment depression on the electrocardiogram (≥ 0.1 mV at 0.08 second after the J point in at least 1 precordial lead). Patients with concomitant cardiovascular disease were excluded from the study. With the exception of low-dose β blocker, which had been continued in 3 of the 8 patients in the short-term study, no drugs capable of affecting the measured parameters were permitted. Nitrates and calcium antagonists were discontinued at least 5 half-lives before the studies. If required, 0.8 mg nitroglycerin was given sublingually. All patients had given their informed written consent before participation in the study.

Study protocol: Both the short- and long-term studies were carried out with a randomized, double-blind, crossover, placebo-controlled protocol. In the short-term study, the extent and duration of action were assessed on 3 days of testing, each separated from the subsequent day by a 24-hour placebo-washout period, on which either placebo or 50 or 100 mg IS-5-MN SR was given. Exercise testing was carried out at 3, 8 and 12 hours after drug/placebo on the respective days of treatment. In the long-term study, after an initial 3- to 4-day placebo run-in phase, there were 3 treatment periods of 3

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TABLE I Antiischemic and Hemodynamic Effects After Initial Administration of IS-5-MN and Placebo

Hours After Administration	3			8			12		
IS-5-MN SR/Placebo	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg
ST ↓ at comparable workload (mm)	2.00 ± 0.09	0.16 ± 0.04*	0.26 ± 0.31*	2.11 ± 0.15	0.91 ± 0.14*	0.72 ± 0.19*	2.20 ± 0.15	1.52 ± 0.22*	1.19 ± 0.36*
Ischemia-free exercise time (s)	90 ± 30	240 ± 26*	241 ± 26*	90 ± 26	180 ± 28*	218 ± 31*	90 ± 26	143 ± 20*	188 ± 31*
Exercise time to 1 mm ST ↓ (s)	150 ± 26	240	260 ± 13	150 ± 26	248 ± 24	264 ± 29	150 ± 26	202 ± 20	249 ± 34
No. of pts without ischemia	(n = 8)	(n = 1)	(n = 3)	(n = 8)	(n = 8)	(n = 5)	(n = 8)	(n = 8)	(n = 7)
Mean arterial BP (mm Hg)	Rest 100 ± 2	97 ± 1	95 ± 1	99 ± 3	97 ± 1	96 ± 1	98 ± 3	98 ± 3	97 ± 2
Heart rate (beats/min)	Ex 122 ± 3	116 ± 2	119 ± 1	121 ± 1	114 ± 2	116 ± 2	122 ± 2	116 ± 2	117 ± 2
	Rest 64 ± 1	65 ± 1	67 ± 1	62 ± 1	64 ± 1	64 ± 1	63 ± 1	65 ± 1	66 ± 1
	Ex 120 ± 3	122 ± 2	123 ± 2	177 ± 1	119 ± 2	120 ± 1	120 ± 3	121 ± 3	122 ± 3

* p < 0.001 vs placebo.

Values are mean ± standard error of the mean.

BP = blood pressure; Ex = exercise at comparable workload, SR = sustained release; ST ↓ = ST-segment depression.

weeks, each separated from the next by a 1-week placebo-washout phase, during which the patients received either placebo or 50 or 100 mg IS-5-MN SR. On the first and the twenty-first day of the respective treatment periods, both before and at 3 and 6 hours after administration, exercise-testing was performed and blood was drawn for plasma concentration determinations.

Exercise testing was conducted in the semisupine position on a revolutions/min-independent bicycle ergometer with an individual workload chosen such that, for a given patient, at 3 to 4 minutes after beginning, ST-segment depression of at least 0.1 mV could be anticipated. At intervals of 3 minutes the workload was increased by 30 watts. Termination of exercise was symptom-limited (angina pectoris, exhaustion, shortness of breath) or on observation of 3 mm of ST-segment depression. Electrocardiographic tracings of the precordial leads V₁ to V₆ were recorded each minute during and for 6 minutes after termination of exercise. Blood pressure and heart rate were measured at rest, at the end of each workload, at termination of exercise and at 3 and 6 minutes after exercise. ST-segment depression at 0.08 second after the J point in the lead with the most marked changes in the pretreatment phase was evaluated by 2 independent observers.

For determination of IS-5-MN plasma concentrations, blood samples were drawn in heparinized containers and centrifuged at 4,000 revolutions/min at 4°C, then frozen at -20°C. The IS-5-MN concentration was analyzed by means of gas chromatography electron capture detection.

Endpoint parameters assessed were reduction in ST-segment depression at comparable workload, ischemia-free exercise time (exercise time with no ST-segment depression), exercise time to onset of 1 mm of ST-segment depression, and heart rate and blood pressure at rest and at comparable workloads, as well as the IS-5-MN plasma concentrations.

Statistical analysis was carried out with the *t* test for paired samples. A *p* value < 0.05 was considered significant.

RESULTS

Short-term study: EXERCISE-INDUCED ST-SEGMENT DEPRESSION: At 3 hours after initial administration of 50 and 100 mg IS-5-MN SR there were comparable reductions in ST-segment depression of 92 and 87% (Table I). At 8 hours, with reductions of 57 and 66%, respectively, the higher dose showed a tendency to more marked effects and at 12 hours, with reductions of 31 and 46%, the action of 100 mg was significantly greater than that of 50 mg.

ISCHEMIA-FREE EXERCISE TIME: Three hours after administration, both 50 and 100 mg IS-5-MN SR had comparably marked increases in ischemia-free exercise time of 167 and 168%, respectively. At 8 hours, with increases of 100 and 142%, respectively, the higher dose showed a tendency to more marked effects. At 12 hours, with increases of 59 and 108%, the action of 100 mg was again significantly greater.

EXERCISE TIME TO ONSET OF 1 MM ST-SEGMENT DEPRESSION: At 3 hours after the 50 mg dose, 7 of the 8 patients were ischemia-free at termination of exercise; at 8 and 12 hours all patients had evidence of ischemia. The exercise time to onset of 1 mm ST-segment depression increased 65 and 35%, respectively. After the 100 mg dose, 5 patients were ischemia-free at termination of exercise at 3 hours, 3 patients at 8 hours and 1 patient at 12 hours. In those patients with evidence of ischemia, exercise time to onset of 1 mm ST-segment depression increased 117% at 3 hours, 110% at 8 hours and 62% at 12 hours.

HEART RATE AND BLOOD PRESSURE: With changes ranging between 2 and 6%, neither dosage led to significant effects on blood pressure or heart rate at rest or during exercise.

Long-term study: EXERCISE-INDUCED ST-SEGMENT DEPRESSION: At 3 hours after initial administration of 50 and 100 mg IS-5-MN SR there were reductions in ST-segment depression of 59 and 62%, respectively. At 6 hours (47 and 55%) they were nearly undiminished (Table II). After 3 weeks of treatment, at 3 hours after both dosages there were comparably marked reductions

TABLE II Plasma Concentrations, Antiischemic and Hemodynamic Effects After Initial Administration (day 1) and During Long-Term Treatment (day 21) with IS-5-MN and Placebo

Hours After Administration	Day 1						Day 21					
	3			6			3			6		
	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg
IS-5-MN SR/Placebo												
ST [†] at Comparable Workload (mm)	1.65 ± 0.16	0.67 ± 0.09*	0.63 ± 0.10*	1.70 ± 0.16	0.90 ± 0.16*	0.76 ± 0.13*	1.85 ± 0.25	0.85 ± 0.13*	0.45 ± 0.09*	2.26 ± 0.34	1.17 ± 0.26*	0.99 ± 0.13*
Ischemia-free exercise time (s)	126 ± 25	215 ± 33*	261 ± 41*	105 ± 26	192 ± 38*	240 ± 43*	111 ± 26*	174 ± 29*	228 ± 29*	99 ± 22	180 ± 31*	216 ± 33*
Exercise time to 1 mm ST [†] (s)	186 ± 26 (n = 10)	230 ± 29 (n = 6)	296 ± 29 (n = 8)	186 ± 26 (n = 10)	225 ± 32 (n = 8)	240 ± 34 (n = 7)	186 ± 26 (n = 10)	223 ± 34 (n = 9)	260 ± 47 (n = 6)	186 ± 26 (n = 10)	240 ± 33 (n = 9)	257 ± 40 (n = 7)
No. of pts without ischemia	0	4	2	0	2	3	0	1	4	0	1	3
Mean Arterial BP (mm Hg)	100 ± 3	95 ± 2	92 ± 2	99 ± 3	97 ± 2	99 ± 1	104 ± 3	101 ± 2	96 ± 2	103 ± 3	101 ± 3	96 ± 3
Heart Rate (beats/min)	126 ± 4	120 ± 4	121 ± 3	125 ± 4	123 ± 3	124 ± 3	127 ± 3	124 ± 3	124 ± 4	128 ± 4	128 ± 3	124 ± 3
Plasma Concentration IS-5-MN (ng/ml)	72 ± 1	75 ± 1	75 ± 1	72 ± 1	73 ± 1	74 ± 1	72 ± 1	80 ± 2	76 ± 1	77 ± 2	79 ± 1	76 ± 2
	123 ± 2	125 ± 1	120 ± 2	121 ± 1	126 ± 2	124 ± 2	119 ± 2	124 ± 2	123 ± 2	127 ± 2	129 ± 2	123 ± 2
	0	312 ± 14	711 ± 62	0	308 ± 17	2824 ± 70	78 ± 35 [†]	386 ± 32	794 ± 90	0	404 ± 44	886 ± 94

* p < 0.001 vs placebo; baseline values of (†) 50 mg and (‡) 100 mg.
Values are mean ± standard error of the mean.
Abbreviations as in Table I.

in ST-segment depression: 55 and 75%, respectively. At 6 hours they were to 48 and 56%, respectively.

ISCHEMIA-FREE EXERCISE TIME: At 3 hours after initial administration of 50 and 100 mg IS-5-MN SR there were increases in the ischemia-free exercise time of 71 and 107%, respectively. At 6 hours this amounted to 83 and 129%. After 3 weeks of long-term treatment, there were comparable increases in ischemia-free exercise time at 3 hours of 57 and 105%, respectively, and at 6 hours this amounted to 82 and 118%.

EXERCISE TIME TO ONSET OF 1 MM ST-SEGMENT DEPRESSION: After initial administration of 50 and 100 mg IS-5-MN SR, 4 and 2 patients, respectively, were free of ischemia at 3 hours as well as 2 and 3 patients at 6 hours. In the remaining patients, there were increases in exercise time to onset of 1 mm ST-segment depression of 43 and 64%, respectively, at 3 hours as well as 46 and 107% at 6 hours. After 3 weeks of long-term treatment, 1 and 4 patients, respectively, were free of ischemia at 3 hours as well as 1 and 3 patients at 6 hours. In the remaining patients there were increases of 37 and 63%, respectively, at 3 hours as well as 47 and 71% at 6 hours.

BLOOD PRESSURE AND HEART RATE: After both dosages the changes observed ranged only between 2 and 8%. None of these was statistically significant compared with placebo at any time of exercise testing.

ISOSORBIDE-5-MONONITRATE PLASMA CONCENTRATION: After initial administration of 50 and 100 mg IS-5-MN SR, the plasma concentrations were 312 and 711 ng/ml, respectively, at 3 hours and 308 and 824 ng/ml at 6 hours. After 3 weeks of treatment, from baseline values (24 hours after the last drug administration) of 78 and 119 ng/ml, respectively, renewed administration of the 50 and 100 mg doses led to increases in the IS-5-MN plasma concentration to 386 and 794 ng/ml at 3 hours and to 404 and 886 ng/ml at 6 hours.

DISCUSSION

This investigation was undertaken to determine the extent and duration of antiischemic effects of 50 and 100 mg IS-5-MN SR. We also sought to determine whether tolerance develops during long-term treatment with the once-daily administration of these dosages. Both dosages show marked antiischemic effects persisting significantly versus placebo throughout the 12-hour period of testing. The 100 mg dose, at 12 hours still eliciting >50% of its maximum, proved significantly more effective at this time than the 50 mg dose. We can assume that it offers the additional advantage of an even longer duration of action. After 3 weeks of treatment, compared with the acute effect, the antiischemic action was documented to be equivalent. Accordingly, there is no evidence for tolerance development. The increase in physical exercise capacity with short- and long-term treatment is indicated by the virtually identical prolongation of the ischemia-free exercise time.

To provide objective evidence for treatment effectiveness, the test parameters chosen were of substantial importance. In our opinion, the most reliable, and those

least amenable to subjective influence, are the ST-segment depression at identical workloads and the ischemia-free exercise time. The absolute exercise time without reference to a measurable parameter such as ischemia is less suited as an endpoint because termination of exercise is frequently caused by subjective factors such as fatigue, shortness of breath or muscular weakness and even angina pectoris is strongly dependent on the prevailing individual threshold for pain perception.

The cause of tolerance development to the antiischemic effect of nitrates is thought to be the continuously high plasma concentration⁴⁻⁶ rendered by oral administration of nitrates in regular intervals 3 or 4 times daily or by uninterrupted transdermal patch treatment.⁷⁻¹³ To avoid tolerance development during long-term treatment with nitrates, as we^{2,14} have shown in studies with various dosing regimens, marked fluctuations in the IS-5-MN plasma concentration within the 24-hour treatment cycle are essential. The interval treatment derived from these findings demands a substantial decrease in the nitrate concentrations during the 24-hour period.^{4,6} This enables regeneration of the cellular mechanism for nitrate-mediated vasodilation such that, on renewed administration, in association with a marked increase in the plasma concentration (which in our experience must be at least 2.7-fold), unattenuated responsiveness is maintained during long-term treatment.^{2,14} Regimens for interval treatment with documented effectiveness during long-term treatment are the once-daily administration of a high dose of isosorbide dinitrate SR and the use of a low-dose transdermal patch system with a 12-hour patch-free interval.^{2,15,16} The importance of an adequately long treatment-free interval is underscored by studies reporting an already appreciable attenuation with twice-daily administration with a 12-hour dosing interval.¹⁷⁻¹⁹ In the present study, during long-term treatment, analysis of the IS-5-MN plasma concentrations shows that 24 hours after the last drug administration there is a decrease of the baseline values to 78 and 119 ng/ml, respectively. This enables, after renewed administration of the same nitrate dose, a 5- to 7-fold increase to levels only slightly higher than those seen after the initial administration; meaningful accumulation does not occur.

Use of intermittent treatment may suggest the following question. To what extent are the patients at risk in the absence of antiischemic protection during the therapeutic gap associated with the low-nitrate or nitrate-free period at night? ST-Holter monitoring studies in patients with stable angina pectoris have shown that approximately 80% of ischemic episodes are detected within a 12-hour period of everyday activities between 6

A.M. and 6 P.M. With the long-acting, marked effect of both dosages used in this study, which for the 100 mg dose can be assumed to exceed 12 hours, and with facilitated compliance through once-daily administration of IS-5-MN SR unattenuated during long-term treatment, an effective antiischemic protection can be provided for the daily period encompassing most physical activities.

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Effects of Isoproterenol on Accessory Pathway Conduction in Intermittent or Concealed Wolff-Parkinson-White Syndrome

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The effects of isoproterenol on accessory pathway conduction were evaluated in 24 patients with intermittent and 60 patients with concealed pre-excitation, using atrial and ventricular incremental and extrastimulus testing techniques. The atrial paced cycle length that induced block in the accessory pathway could be compared in 11 of the 24 patients with intermittent preexcitation before and after isoproterenol; it decreased from 622 ± 212 ms to 408 ± 128 ms (mean $\pm$ standard deviation) after isoproterenol ($p < 0.01$). The anterograde effective refractory period of the accessory pathway could be compared in 5 patients before and after isoproterenol; it decreased from 460 ± 131 to 310 ± 48 ms after isoproterenol ($p < 0.01$). None of the 60 patients with concealed preexcitation showed ventricular preexcitation with isoproterenol infusion. Eighty-one of the 84 patients had clinically documented supraventricular tachycardia, suggesting the accessory pathway was capable of retrograde conduction. Retrograde study was performed in all 84 patients; 83 had retrograde conduction and the other had no retrograde conduction before and after isoproterenol. The ventricular paced cycle length that induced block in the accessory pathway could be compared in 38 patients before and after isoproterenol; it decreased from 342 ± 71 to 296 ± 39 ms after isoproterenol ($p < 0.001$). The retrograde effective refractory period of the accessory pathway could be compared in 56 patients; it decreased from 293 ± 76 to 238 ± 36 ms after isoproterenol ($p < 0.001$). In conclusion, isoproterenol facilitates anterograde and retrograde accessory pathway conduction, but the facilitation of anterograde conduction occurs only in those capable of spontaneous conduction.

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Sympathetic tone is known to enhance antero-grade and retrograde conduction of the accessory pathway in Wolff-Parkinson-White syndrome.¹⁻⁴ Both treadmill exercise and isoproterenol infusion shorten the refractory period of the accessory pathway and increase the ventricular rate during atrial fibrillation.⁵⁻⁸ Patients with Wolff-Parkinson-White syndrome, having a constant preexcitation and a short anterograde accessory pathway refractory period, are thought to be at risk for dangerously rapid ventricular rate during atrial fibrillation that could lead to ventricular fibrillation.^{9,10} Patients with intermittent preexcitation, on the other hand, are felt to be safe.¹¹ However, a rapid accessory pathway conduction could possibly occur during exercise if sympathetic tone could enhance conduction in these patients.^{3-5,7,8,12} Little is known regarding the effect of sympathetic tone on anterograde conduction of the accessory pathway in patients with intermittent or concealed Wolff-Parkinson-White syndrome. Thus, we performed a systematic study to elucidate the effects of isoproterenol infusion on conduction properties of the accessory pathway in patients with intermittent or concealed Wolff-Parkinson-White syndrome.

METHODS

Patients: The study population was comprised of 24 patients with intermittent ventricular preexcitation and 60 patients with atrioventricular reentrant tachycardia incorporating a concealed accessory pathway. Twenty-one of the 24 patients with intermittent ventricular preexcitation had clinically documented paroxysmal supraventricular tachycardia, while the other 3 patients had atrial fibrillation or syncope. There were 56 men and 28 women aged between 15 and 73 years (median 42). No patient had organic heart disease. The study protocol was reviewed and approved by the institutional committee on human research.

Electrophysiologic studies: Electrophysiologic studies were performed in the postabsorptive, nonsedated state after obtaining written informed consent. All cardiac medicines were discontinued at least 72 hours (or 5 plasma half-lives) before the study. The His bundle electrocardiogram was recorded from a 6Fr quadripolar electrocatheter introduced percutaneously via the right femoral vein and positioned across the tricuspid valve. A second 5Fr bipolar electrocatheter was positioned at the right ventricular apex for pacing. A third 7Fr octopolar electrocatheter was introduced via the right antecubital vein by a small incision and advanced to the coronary

sinus. In this position the 4 proximal electrodes were against the lateral wall of the right atrium near the junction of the superior vena cava, and the 4 distal electrodes were in the coronary sinus. The distal 4 electrodes were used for recording the left atrial electrocardiogram from different sites of coronary sinus and for pacing from the coronary sinus; the proximal 4 electrodes were used for recording the right atrial electrocardiogram and for right atrial pacing. Surface electrocardiographic leads I, aVF and V_1 , as well as intracardiac electrocardiograms, were simultaneously displayed and recorded on a multichannel oscilloscopic photographic recorder (VR-16, Electronics for Medicine) at a paper speed of 100, 150 and 250 mm/s, using a filter setting between 30 and 500 Hz. Stimulus of 2 ms in duration and approximately twice the diastolic threshold was provided by a digital programmable stimulator (DTU PG 100, Bloom Associates).

The study protocol consisted of incremental atrial pacing to an atrial paced rate that induced atrioventricular block, atrial extrastimulus testing at an atrial driven cycle length of 500 or 400 ms, incremental ventricular pacing to a ventricular paced rate that induced ventriculoatrial block or to a paced cycle length of 260 ms, and ventricular extrastimulus testing at a ventricular driven cycle length of 500 or 400 ms. Retrograde accessory pathway conduction during supraventricular tachycardia was inferred by an abnormal atrial activation sequence, by an increase in ventriculoatrial interval or cycle length of tachycardia with development of bundle branch block ipsilateral to the accessory pathway and by the ability to capture the atria with a critically timed ventricular extrastimulus given during induced tachycardia when the His bundle was refractory.^{13,14} After completion of the control study, each patient was given an intravenous isoproterenol infusion at a dose ranging between 0.5 and 6 $\mu\text{g}/\text{min}$ (mean $\pm$ standard deviation 1.9 ± 0.9) to increase the sinus rate to approximately 120 beats/min (sinus cycle length decreased from 743 ± 148 to 546 ± 109 ms with an average decrease of 27% and the range of decrease between 11 and 50%). Electrophysiologic studies were repeated 5 minutes later while the patient was receiving constant isoproterenol infusion.

Conduction intervals and refractory periods were measured and defined as previously described.^{13,14} The data are expressed as mean $\pm$ standard deviation and the Student *t* test for paired data was used for statistical analysis.

RESULTS

Effects of isoproterenol on anterograde accessory pathway conduction: In the 24 patients with intermittent ventricular preexcitation, 2 showed stable ventricular preexcitation during sinus rhythm before isoproterenol, and both showed stable preexcitation after isoproterenol. Nine patients showed intermittent ventricular preexcitation with both normal and preexcited QRS complexes during sinus rhythm before isoproterenol, 5 of these 9 patients showed stable preexcitation, 2 showed intermittent preexcitation and 2 showed no

TABLE I Ventricular Preexcitation Before and After Isoproterenol

	Control	Isoproterenol
Intermittent preexcitation		
Stable preexcitation	2	8
Intermittent preexcitation	9	5
No preexcitation	13	11
Concealed	60	60

preexcitation after isoproterenol. Thirteen patients showed no ventricular preexcitation during sinus rhythm before isoproterenol, 1 of these 13 patients showed stable preexcitation, 3 showed intermittent preexcitation and 9 showed no preexcitation after isoproterenol. In the 60 patients with a concealed accessory pathway, none showed ventricular preexcitation with isoproterenol infusion (Table I).

The longest atrial paced cycle length that induced anterograde block in the accessory pathway could be compared in 11 of the 24 patients with intermittent ventricular preexcitation before and after isoproterenol infusion. It decreased from 622 ± 212 to 408 ± 128 ms after isoproterenol ($p < 0.01$) (Figure 1). The anterograde effective refractory period of the accessory pathway could be compared in 5 of the 24 patients with intermittent ventricular preexcitation before and after isoproterenol infusion. It decreased from 460 ± 131 to 310 ± 48 ms after isoproterenol ($p < 0.01$).

Effects of isoproterenol on the retrograde accessory pathway conduction: In the 3 patients with intermittent ventricular preexcitation and without a clinical history of paroxysmal supraventricular tachycardia, 1 did not show ventriculoatrial conduction via the accessory pathway before and after isoproterenol infusion, and 2 showed ventriculoatrial conduction via the accessory pathway before and after isoproterenol infusion. In the 21 patients with intermittent ventricular preexcitation and with clinically documented paroxysmal supraventricular tachycardia, all had ventriculoatrial conduction via the accessory pathway before and after isoproterenol infusion. In the 60 patients with atrioventricular reentrant tachycardia incorporating a retrogradely conducting accessory pathway before isoproterenol, all had ventriculoatrial conduction via the accessory pathway after isoproterenol.

The longest ventricular paced cycle length that induced retrograde block in the accessory pathway could be compared before and after isoproterenol infusion in 38 patients with intermittent ventricular preexcitation (10 patients) or a concealed accessory pathway (28 patients). It decreased from 342 ± 71 to 296 ± 39 ms after isoproterenol ($p < 0.001$). The retrograde effective refractory period of the accessory pathway could be compared before and after isoproterenol infusion in 56 patients with intermittent ventricular preexcitation (12 patients) or a concealed accessory pathway (44 patients). It decreased from 293 ± 76 to 238 ± 36 ms after isoproterenol ($p < 0.001$).

Effects on supraventricular tachycardia: In the 24 patients with intermittent preexcitation, sustained or-

thodromic atrioventricular reentrant tachycardia was inducible in 19 patients before isoproterenol; all 19 patients had induction of sustained tachycardia after isoproterenol. Three patients had induction of nonsustained atrioventricular reentrant tachycardia before isoproterenol, 2 of these 3 patients had induction of sustained tachycardia and the other had induction of nonsustained tachycardia after isoproterenol. Two patients had no induction of atrioventricular reentrant atrial echo before isoproterenol; 1 of these 2 patients had induction of nonsustained tachycardia, and the other had no induction of echo after isoproterenol.

In the 60 patients with concealed accessory pathway, sustained atrioventricular reentrant tachycardia was inducible in 43 patients before isoproterenol; 41 of these 43 patients had induction of sustained tachycardia, 1 had induction of echo and the other had no induction of echo after isoproterenol. Eleven patients had induction of nonsustained atrioventricular reentrant tachycardia before isoproterenol; 9 of these 11 patients had induction of sustained tachycardia and 2 had induction of

nonsustained tachycardia after isoproterenol. Three patients had induction of atrioventricular reentrant atrial echo before isoproterenol, 1 of these 3 patients had induction of sustained tachycardia, 1 had induction of nonsustained tachycardia and the other had no induction of echo after isoproterenol. Three patients had no induction of atrioventricular reentrant atrial echo before isoproterenol; 1 of these 3 patients had induction of echo, and the other 2 had no induction of echo after isoproterenol.

The cycle length of tachycardia was compared in the 59 patients with sustained tachycardia before and after isoproterenol infusion; it decreased from 370 ± 55 to 281 ± 32 ms after isoproterenol ($p < 0.001$). Shortening in cycle length of tachycardia resulted primarily from a shortening in AH interval from 192 ± 47 to 125 ± 37 ms ($p < 0.001$).

DISCUSSION

Autonomic tone and ventricular preexcitation: Modulation of the accessory pathway conduction by

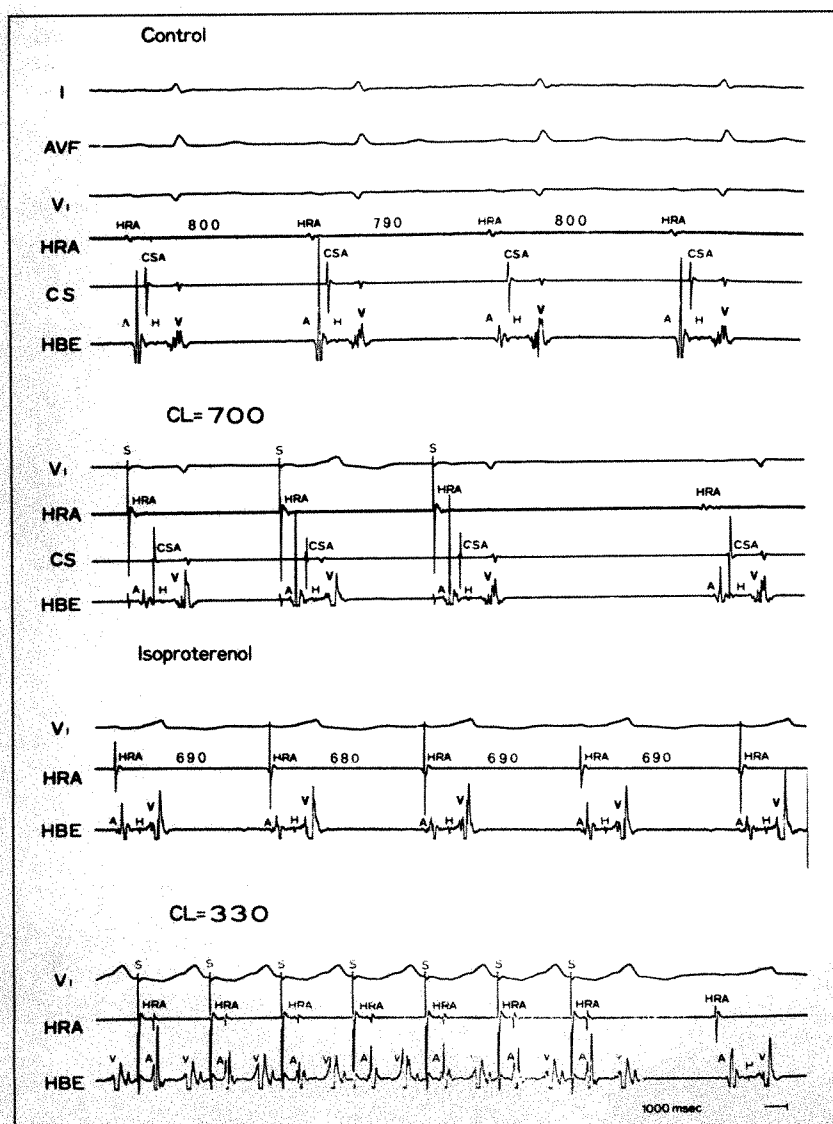


FIGURE 1. A patient with intermittent ventricular preexcitation in whom pre-excitation became stable after isoproterenol infusion. *Top*, sinus rhythm with a normal PR interval and narrow QRS complex during control. *Upper middle*, intermittent preexcitation during atrial pacing at a cycle length of 700 ms during control. *Lower middle*, stable preexcitation with isoproterenol. *Bottom*, stable preexcitation during atrial pacing at a cycle length of 330 ms with isoproterenol. A = low septal right atrial response to sinus or paced beat; CS = coronary sinus electrogram; CSA = left atrial response recorded from coronary sinus; H = His bundle response to sinus or paced beat; HBE = His bundle electrogram; HRA = high right atrial response to sinus or paced beat; S = stimulus artifact; V = ventricular response to sinus or paced beat.

autonomic tone has been noted since the description of the Wolff-Parkinson-White syndrome in 1930. Wolff et al¹⁵ observed that vagal stimulation favored the occurrence of ventricular preexcitation. Subsequently, Wolff,¹⁶ Averill,¹ Sandberg,¹⁷ Strasberg¹⁸ and their co-workers observed normalization of QRS complexes during exercise in patients with ventricular preexcitation. Averill,¹ Weisfogel² and their co-workers further noticed that in 2 patients with normal PR interval an unexpected ventricular preexcitation developed during exercise. Recently, Przybylski et al³ studied 21 patients with normal PR interval, in whom at least 1 previous electrocardiogram showed ventricular preexcitation. They demonstrated the appearance of ventricular preexcitation in 9 of 21 patients when sinus rate was slowed with carotid massage. Ventricular preexcitation appeared in an additional 5 patients when isoproterenol infusion along with carotid massage was performed in the remaining 12 patients. Easley et al⁴ reported a patient with intermittent preexcitation and recurrent exertional syncope, in whom the anterograde conduction of the accessory pathway was markedly enhanced with isoproterenol infusion that resulted in the occurrence of rapid antidromic reciprocating tachycardia associated with syncope. These studies suggest that a prolonged refractory period in the accessory pathway can produce a rate-dependent block resulting in a normal PR interval during sinus rhythm. Ventricular preexcitation can be brought out by vagal stimulation when the heart rate is slowed. These studies also suggest that depressed accessory pathway conduction can be facilitated by catecholamines during exercise or with isoproterenol infusion.

Effects of isoproterenol or epinephrine on accessory pathway conduction and atrioventricular reentrant tachycardia: Wellens,⁵ Brugada¹⁹ and their co-workers evaluated the effects of isoproterenol on the anterograde accessory pathway conduction and the initiation of atrioventricular reentrant tachycardia in patients with the Wolff-Parkinson-White syndrome with or without long-term oral amiodarone therapy. They found isoproterenol shortened the anterograde effective refractory period of the accessory pathway. The greatest amount of shortening was noted in those patients with the longest initial value for the anterograde accessory pathway refractory period. Morady et al⁶ evaluated the effects of epinephrine on atrioventricular reentrant tachycardia treated with quinidine or verapamil. They found epinephrine shortened the atrial paced cycle length that induced block in the accessory pathway, the anterograde accessory pathway effective refractory period, the ventricular paced cycle length that induced block in the accessory pathway and the retrograde accessory pathway effective refractory period. They also demonstrated a marked shortening in the mean RR interval and the shortest RR interval during induced atrial fibrillation with infusion of epinephrine. Epinephrine enhanced atrioventricular nodal conduction and facilitated induction of atrioventricular reentrant tachycardia. Thus, both isoproterenol and epinephrine facilitate anterograde and retrograde accessory pathway conduction and

may partially reverse the depressant effects of amiodarone or quinidine on the accessory pathway.

Effects of isoproterenol on intermittent preexcitation and concealed accessory pathway: The present study is in accord with the previous study of Przybylski et al³ and the case report by Easley et al⁴ in that isoproterenol infusion facilitated the anterograde accessory pathway conduction in patients with intermittent ventricular preexcitation. Although isoproterenol increases the sinus rate and could produce a rate-dependent block in the accessory pathway, it improves the conduction in the depressed accessory pathway and thus facilitates the accessory pathway conduction. Our finding may in part explain the clinical observation in some patients with intermittent ventricular preexcitation in whom variation in sympathetic tone causes a marked variation in the anterograde accessory pathway effective refractory period. Although intermittent preexcitation is considered to be a "good finding" with low risk of sustaining a "dangerous" ventricular rate during atrial fibrillation,^{11,20} our finding suggests caution in the management of patients with intermittent ventricular preexcitation and paroxysmal atrial fibrillation. A rapid ventricular rate, although unlikely, could possibly result from fast anterograde accessory pathway conduction when sympathetic tone is triggered by anxiety, hypotension or other factors.^{4,5,8,12} The present study also demonstrates that the facilitation of anterograde accessory pathway conduction occurs only in those capable of spontaneous anterograde accessory pathway conduction. Isoproterenol does not bring out ventricular preexcitation in patients with concealed accessory pathways in whom ventricular preexcitation has not occurred before. This finding suggests that a unidirectional block of the accessory pathway in concealed Wolff-Parkinson-White syndrome is likely to be an intrinsic property of the accessory pathway, resulting from anatomic or functional factors, rather than from a marked prolongation of the refractory period.

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Validation and Applications of Mitral Prosthetic Valvular Areas Calculated by Doppler Echocardiography

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Doppler echocardiography is used in the non-invasive evaluation of mitral valve prostheses using parameters heretofore validated primarily for native valves. Accordingly, this study was designed to examine the validity and relative usefulness of valve gradient and area measurements in a group of 26 patients (17 women, 9 men, mean age 62 ± 8 years), 19 ± 4 months after implantation of different sizes (25 to 31 mm) of a given type of bio-prosthesis. Areas obtained with both the continuity equation, using stroke volume measured in the left ventricular outflow tract, and the pressure half-time method are compared to known prosthetic areas derived from an in vitro hydraulic model. Areas calculated by the continuity equation correlate well with in vitro areas ($r = 0.82$, standard error of the y estimate = 0.1 cm^2 , $p < 0.001$), and are within the range of predicted in vitro values in 92% of cases. Areas derived by the pressure half-time method do not correlate with in vitro areas ($r = 0.15$, $p > 0.3$) or continuity equation areas ($r = 0.23$, $p > 0.2$), and are above the range of predicted values in 69% of cases. Correlations are also found between continuity equation areas and the peak and mean valvular gradients ($r = 0.59$, $p < 0.005$ and $r = -0.63$, $p < 0.0005$, respectively). Taking the effect of cardiac output on gradients into account results in projected relations between indexed prosthetic areas and the pressure gradients at rest and during exercise.

These data show that the continuity equation, as applied in this study, is a valid method for assessing mitral valve bioprosthetic areas provided that there is no significant aortic or mitral regurgitation. The pressure half-time method is not valid in this situation and grossly overestimates the area in many cases. The projected relations between indexed prosthetic areas and pressure gradients may be helpful for prosthesis selection to avoid a patient-prosthesis mismatch.

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Doppler echocardiography is currently used for the noninvasive evaluation of mitral valve prostheses. The parameters most often measured with this technique are the peak and mean valvular gradients, as well as the effective orifice area.¹⁻⁶ Validation of the latter has been derived mainly from comparison with hemodynamic data in patients with native valve disease and there has been little validation in patients with mitral valve prostheses. Moreover, recent studies have shown that there are limitations to the pressure half-time method, which is currently the most commonly used method to calculate mitral valve orifice area.⁷⁻⁹

Our goals were to assess the validity of Doppler echocardiographic measurements, particularly effective orifice area calculations, in patients with mitral valve prostheses, and to determine the implications of such information with regard to prosthetic performance and implantation criteria. For this purpose, effective mitral orifice areas were calculated with Doppler echocardiography in a group of patients with a specific type of bio-prosthesis of varying sizes, using both the continuity equation and pressure half-time methods. These measurements were then compared to known prosthetic effective orifice area values derived from in vitro hydraulic model flow measurements provided by the manufacturer.

METHODS

The study population consisted of 26 patients (17 women and 9 men) with a mean age of 62 ± 8 years (range 44 to 75) who underwent mitral valve replacement at the Quebec Heart Institute between May 21, 1986, and September 23, 1987. Preoperative diagnoses included mitral stenosis (18 patients), mitral insufficiency (5 patients) or mixed mitral valve disease (3 patients). Two patients had severe coronary artery disease and underwent concurrent coronary artery bypass graft surgery. All inserted prostheses were Medtronic Intact™ bioprostheses model 705, and the sizes used were 25 mm (7 patients), 27 mm (11 patients), 29 mm (4 patients) and 31 mm (4 patients).

Doppler echocardiographic examination was performed a mean of 19 ± 4 months after surgery. All studies were performed by the same technician on a Hewlett-Packard Sonos-500 ultrasound system and subsequently independently reviewed by the same investigator. Four patients had to be excluded because of technically inadequate studies. There was complete agreement

TABLE I In Vitro and In Vivo Measurements in Intact Mitral Bioprostheses of Various Sizes

Prosthesis Size (mm)	In Vitro EOA (cm ²)	No. of Pts	In Vivo Measurements by Doppler Echocardiography					Regurgitation (No. of patients [Severity], Incidence)	
			EOA by CE (cm ²)	EOA by PHT (cm ²)	Peak Gradient (mm Hg)	Mean Gradient (mm Hg)		Mitral	Aortic
25	1.34 (1.19–1.48)	7	1.36 ± 0.08 (1.20–1.46)	1.78 ± 0.32 (1.26–2.25)	16.2 ± 3.6 (10.4–21.0)	7.8 ± 2.4 (4.2–12.7)		1(1+), 14%	2(1+), 29%
27	1.51 (1.31–1.71)	11	1.53 ± 0.09 (1.41–1.74)	2.02 ± 0.29 (1.54–2.48)	11.0 ± 3.1 (6.4–18.0)	5.4 ± 1.5 (2.4–7.1)	0	0	4(1+), 30%
29	1.65 (1.43–1.86)	4	1.63 ± 0.08 (1.49–1.69)	2.28 ± 0.62 (1.46–2.93)	8.6 ± 1.5 (7.3–10.9)	3.6 ± 0.4 (3.1–4.0)	0	0	2(1+), 50%
31	1.86 (1.66–2.05)	4	1.81 ± 0.15 (1.54–1.91)	1.87 ± 0.23 (1.51–2.12)	9.0 ± 3.2 (5.4–13.5)	3.6 ± 1.1 (2.4–5.0)	0	0	0

Values are mean ± standard deviation with range of values in parentheses.
CE = continuity equation; EOA = effective orifice area; PHT = pressure half-time.

in measurements between technician and investigator in 19 cases, whereas measurements were redone with a frame-grabber off the videotape in 7 patients. Measurements obtained in patients for the purpose of this study consisted of peak and mean mitral valvular gradients, stroke volume, cardiac output and prosthetic valve area by both the continuity equation and pressure half-time methods. Peak and mean gradients were obtained with pulsed- and continuous-wave Doppler recordings of the mitral jet velocity from the apical window and application of the modified Bernoulli equation as previously described and validated.^{10–12} Using color-flow Doppler as a guide, we took great care to ensure optimal alignment between the Doppler cursor and the mitral flow jet; an angle <20° was considered a minimal requirement and the maximal velocities recorded were used to determine the pressure gradients. Stroke volume was calculated from the left ventricular outflow tract area, as estimated from the corresponding internal diameter measured in the left parasternal long-axis view in systole, multiplied by the velocity-time integral of the left ventricular outflow tract pulsed Doppler signal recorded from the apical long-axis view as previously described.^{13–15} Cardiac output was equal to stroke volume multiplied by the heart rate. Great care was taken to ensure that the diameter was measured perpendicularly to the left ventricular outflow tract, trailing edge to leading edge just proximal to the aortic leaflets. Also, the pulsed Doppler sample was positioned so that the angle between the Doppler cursor and the left ventricular outflow tract was as close to 0° as possible (always <20°) and that the Doppler signal was truly representative of the left ventricular outflow tract flow as emphasized by Skjaerpe et al.¹⁶ Prosthetic valve areas were determined using the pressure half-time method proposed by Hatle et al,¹⁷ and by the continuity equation described by Nakatani et al¹⁸ as follows: $PVA = SV^{LVOT}/VTI$, where SV^{LVOT} is stroke volume in the left ventricular outflow tract, and VTI is the velocity-time integral of the mitral jet Doppler signal. Multiple determinations were done in each patient to ensure reproducibility of measurements; in patients with atrial fibrillation (11 patients),

an effort was made to choose complexes most representative of the average heart rate and, particularly when applying the continuity equation, to evaluate left ventricular inflow and outflow complexes occurring at similar heart rates.

Effective orifice areas for each size of Intact valve were calculated using data provided by the manufacturer (Medtronic Blood Systems), based on studies on a hydraulic model¹⁹ performed at the Georgia Institute of Technology by Dr. A.P. Yoganathan (used with permission). This model measures the transvalvular pressure gradients and pulsatile flow rates at different cardiac outputs, with a pulse rate of 70 beats/min and systole accounting for approximately 35% of the cardiac cycle. From this information, valve areas were calculated using the formula proposed by Yoganathan et al¹⁹ and a range of values was obtained for each prosthesis size, suggesting that effective valve areas increase as a function of the prevailing flow and pressure gradient. The mean value of each in vitro area range (Table I) was used in this study for linear regression analysis against in vivo determinations. The in vitro areas were not available to the echocardiographer at the time of Doppler echocardiographic measurement of the effective orifice areas.

Color-flow mapping was performed in multiple views to interrogate for the presence of mitral or aortic regurgitation. This was visually graded as 1+ when the jet was very narrow and extended only a short distance beyond the valve, and 2+ when the jet was somewhat larger and longer but remained narrow at the level of valvular annulus and did not extend beyond the tip of the anterior mitral valve leaflet (aortic) or first third of the left atrium (mitral). Significant 3+ or 4+ mitral or aortic regurgitation was not observed in our patient population.

Continuous variables are expressed as mean, standard deviation of the mean and range. Statistical analysis of the association of continuous variables was done using the Pearson linear correlation coefficient and standard error of the y estimate. Graphs were constructed with the corresponding linear regression equation.

For statistical inference, p values were obtained using the *t* test for the correlation coefficient and a p value <0.05 was considered significant.

RESULTS

Table I lists the results for areas and gradients, as well as the incidence of valvular regurgitation according to prosthesis size. For the 26 patients, the peak gradient ranged from 5.4 to 21.0 mm Hg (mean 11.9 ± 4.2) and the mean gradient from 2.3 to 12.7 mm Hg (mean 5.5 ± 2.3). Valve areas ranged from 1.20 to 1.91 cm² (mean 1.54 ± 0.17) by the continuity equation and from 1.26 to 2.93 cm² (mean 1.97 ± 0.4) by the pressure half-time method. There is a good correlation ($r = 0.82$) between the mean in vitro area for each bioprosthesis size and the in vivo areas calculated by the continuity equation (Figure 1). The in vivo valve areas calcu-

lated by the pressure half-time method do not, however, correlate significantly with the in vitro valve areas ($r = 0.15$), with overestimations of the known in vitro area range occurring in 18 of 26 cases (69%) (Figure 2). There is similarly no correlation between the pressure half-time and continuity equation methods ($r = 0.23$). A significant correlation is observed between the peak and mean gradients ($r = 0.85$). Correlations of peak and mean gradients with areas are $r = -0.60$ and $r = -0.64$ for in vitro prosthetic areas, $r = -0.59$ and $r = -0.63$ for in vivo continuity equation-derived areas (Figure 3), and $r = -0.05$ and $r = -0.11$ for areas obtained with the pressure half-time method. Cardiac output does not correlate with body surface area ($r = 0.28$, $p > 0.05$) in these patients and cardiac index is significantly lower in the 11 patients with atrial fibrillation than in the 15 patients with normal sinus rhythm

FIGURE 1. Correlation between mean in vitro effective mitral bioprosthesis valve area for each valve size and in vivo mitral bioprosthesis valve area determined by Doppler echocardiography using the continuity equation (CE), with stroke volume measured in the left ventricular outflow tract. The bold line represents the regression line. The dashed lines define the range of area values obtained in vitro. SEE = standard error of the y estimate.

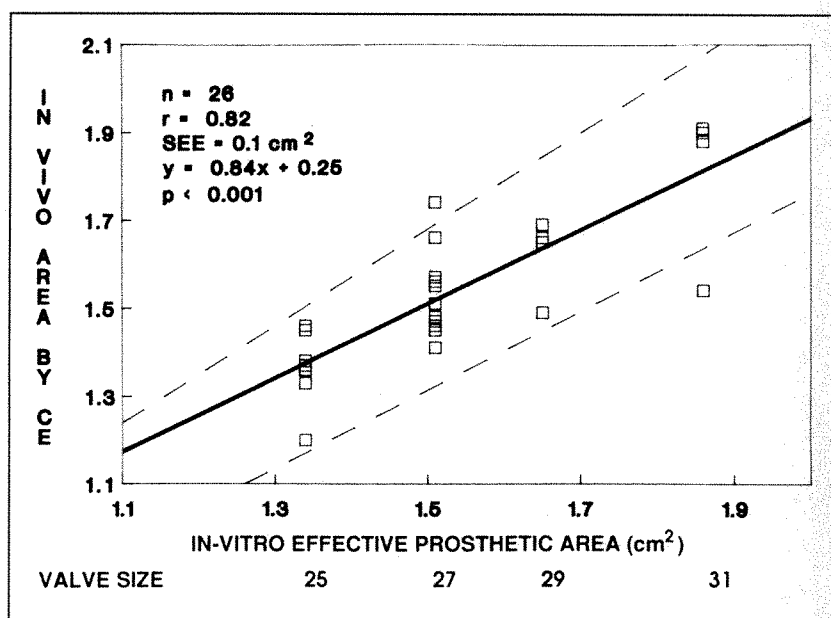
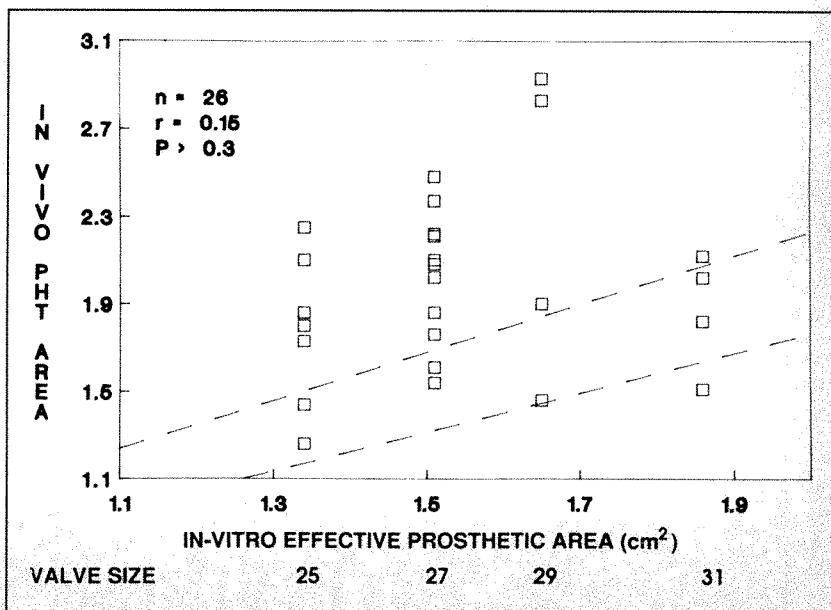


FIGURE 2. Correlation between mean in vitro effective mitral bioprosthesis valve area for each valve size and in vivo mitral bioprosthesis valve area determined by Doppler echocardiography using the pressure half-time method (PHT). The dashed lines define the range of area values obtained in vitro.



(2.4 ± 0.4 vs 3.1 ± 0.6 liters/min/m², $p < 0.01$). Indexing prosthetic areas for body surface area does not improve correlations with peak or mean gradients, but better correlations are obtained if the peak and mean gradients are compared to the prosthetic area divided by cardiac output in the subgroup of patients with normal sinus rhythm ($r = -0.75$ and -0.72 , respectively).

DISCUSSION

Stroke volume as used in the continuity equation was measured in the left ventricular outflow tract for 2 reasons: (1) it is generally agreed that this is probably the most reliable and easily accessible site for cardiac output determinations by Doppler echocardiography^{14,15}; and (2) cardiac output determinations at the level of the mitral annulus are not possible in patients with mitral valve prostheses. This approach is theoretically not valid to measure mitral valve areas in cases with valvular regurgitation, as it would tend to overestimate the valve area in cases with aortic regurgitation

and to underestimate it in cases with mitral regurgitation. No patient in this study had significant (3+ or 4+) valvular regurgitation, but results could have been somewhat influenced by this factor in the patients with 1+ or 2+ regurgitation.

The pressure and flow data provided by the manufacturer suggest that there is not a unique area for each prosthesis size but rather that the effective orifice area tends to be augmented with increasing pressure and flow. This may be due to some leaflet inertia at low flow rates. The relation given in Figure 1 might be improved if it was possible to account more precisely for this factor rather than using the mean in vitro areas for comparison. Nonetheless, the area values obtained in vivo by the continuity equation method are within the range of the predicted in vitro area values in 24 of the 26 cases (92%), whereas there is a slight overestimation in one patient (0.03 cm²) and an underestimation in another (0.12 cm²). The latter might be due to either deterioration of the valve in the 19 ± 4 months since implanta-

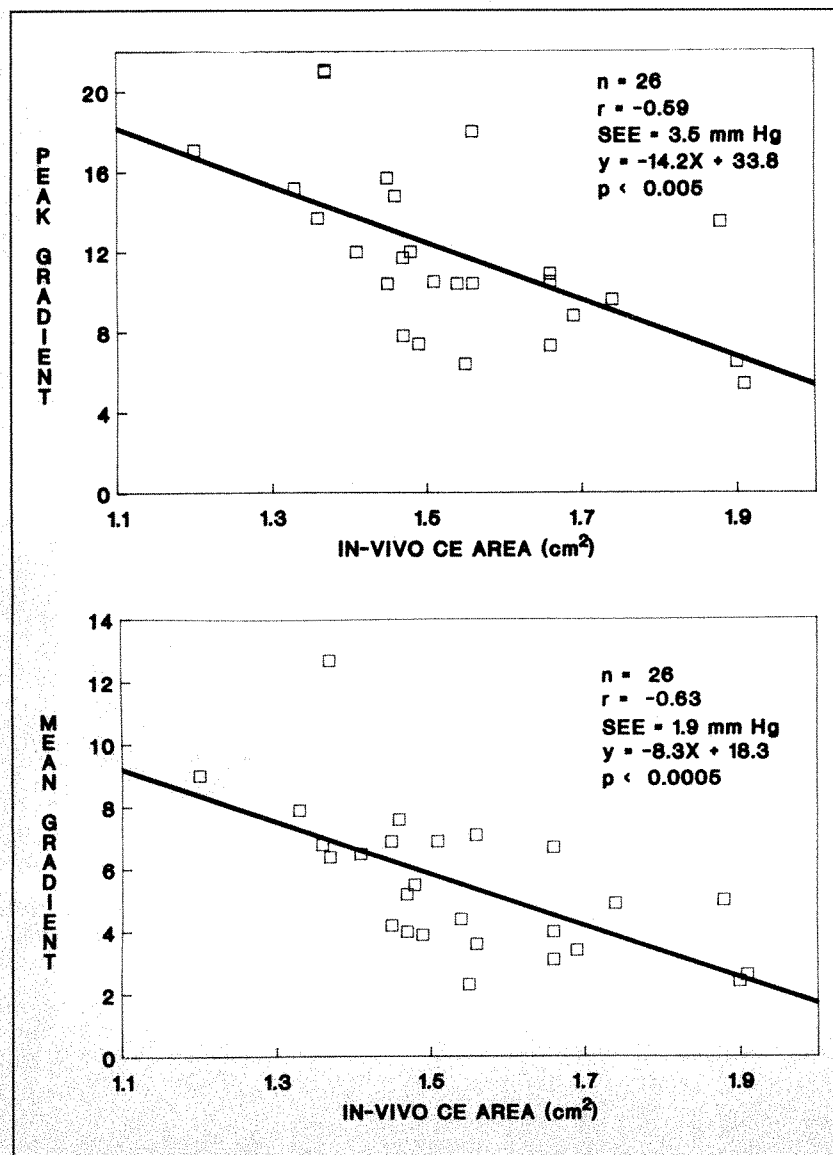


FIGURE 3. *Top*, correlation between mitral bioprosthetic valve area determined by Doppler echocardiography using the continuity equation (CE), with stroke volume measured in the left ventricular outflow tract, and peak transprosthetic gradient (mm Hg) derived from the modified Bernoulli equation. *Bottom*, correlation between mitral bioprosthetic valve area determined by Doppler echocardiography using the CE, with stroke volume measured in the left ventricular outflow tract, and mean transprosthetic gradient (mm Hg) derived from the modified Bernoulli equation. SEE = standard error of the estimate.

tion or to an error in methodology. Overall, the data suggest that the continuity equation, as applied in this study, is valid for assessing mitral valve bioprosthetic areas in the absence of significant valvular regurgitation.

The valve area values calculated by the pressure half-time method do not, however, correlate with the in vitro values and, as demonstrated in Figure 2, this method grossly overestimates the effective valve area in most cases. Notwithstanding an unlikely error in the in vitro methodology, this finding shows that the method is not valid to measure bioprosthetic valve areas and is consistent with recent reports.^{7,18} The pressure half-time method was derived empirically in native valves and subsequent investigators have demonstrated that it may be influenced by many factors other than the valve area^{7,8} and may not be accurate in certain instances, such as after valvuloplasty.⁹ A possible explanation for the overestimation found in most of the patients with bioprosthesis might be the presence of some opening inertia of the prosthesis at the beginning of diastole, resulting in a higher initial gradient and a steeper deceleration slope once the valve has opened. Another might be the sudden change by outside intervention of a single parameter (effective valve orifice area) without enough time for adaptive adjustments to occur in the other parameters known to influence the half-time method.

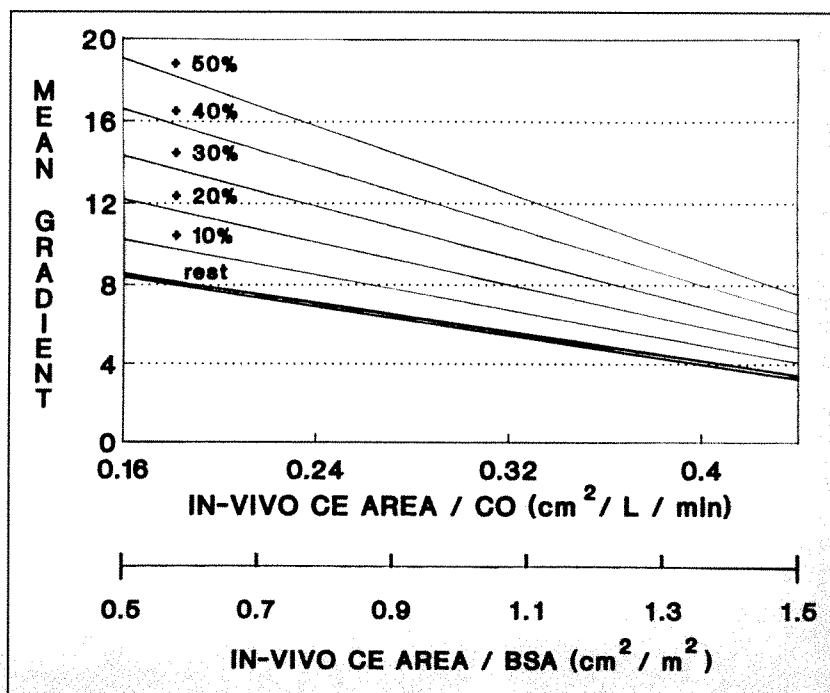
As in previous studies,^{5,6} Table I and Figure 3 show that peak and mean gradients are only grossly correlated to prosthesis size. In this context, it should be emphasized that pressure gradients are determined not only by valve orifice area but also by prevailing cardiac output, which varies from one individual to another depending on body size, hemodynamic status, cardiac rhythm and other factors. Hence, it would appear that valve area determinations are more accurate than gradient mea-

surements in assessing intrinsic prosthetic performance. Nonetheless, pressure gradients are also important because they reflect the increased stroke work created by the prosthesis and they may be unacceptably high, either because of pathologic stenosis, a state of high cardiac output or a mismatch between prosthesis size and body size.²⁰⁻²²

The lack of correlation in this study between cardiac output and body surface area probably reflects a heterogeneity of hemodynamic status in these patients. Using the relation derived between effective prosthesis area divided by cardiac output ($\text{cm}^2/\text{liter}/\text{min}$) and mean gradient in the subgroup of patients with normal sinus rhythm and assuming a normal cardiac index of 3.3 liters/min/ m^2 ,²³ one can nonetheless project (Figure 4) what the relation between effective prosthesis area indexed for body surface area and mean gradient would be in patients with normal cardiac output at rest as well as with 10 to 50% increases of stroke volume such as may occur during maximal upright exercise.²⁴⁻²⁶ Since indexed effective prosthesis area can easily be calculated preoperatively from the in vitro calculated effective orifice area and the patient's body surface area, this relation could be useful in selecting the type and size of prosthesis to be implanted to avoid valve prosthesis-patient mismatch. Further studies are necessary, however, to confirm some of these assumptions as well as their applicability to other types of prostheses.

The performance of this prosthesis with regard to gradients and areas compares to that of other bioprostheses of similar sizes.^{1,3,4} Relatively high resting gradients (mean gradient >5 mm Hg) were found in 13 of 26 patients without evidence of pathologic prosthetic stenosis and are likely due to a mismatch between prosthesis size and body size. These results emphasize that bioprostheses tend to have relatively small orifice

FIGURE 4. The *thick line* indicates the relation between effective prosthetic area divided by cardiac output (CO) ($\text{cm}^2/\text{liter}/\text{min}$) and mean gradient (mm Hg) in patients with normal sinus rhythm ($r = -0.72$). A projection of what the relation between indexed effective prosthetic area (cm^2/m^2 second abscissa) and mean gradient would be in patients with normal cardiac output is obtained by multiplying first abscissa values by an assumed normal cardiac index of 3.3 liters/min/ m^2 . *Thin lines* are relations corresponding to 10 to 50% increases in stroke volume as may occur during upright exercise. BSA = body surface area; CE = continuity equation.



areas,^{27,28} and the type of analysis proposed in Figure 4 could therefore be important to consider. Studies with exercise as well as studies relating prosthesis size to mortality, morbidity and functional class appear necessary to define the minimal requirements in terms of indexed prosthetic area.

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Clinical and Pathologic Study of Familial Dilated Cardiomyopathy

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To evaluate the occurrence of familial cases of dilated cardiomyopathy (DC), 165 consecutive patients were studied. Diagnosis of myocardial disease was based on clinical, hemodynamic, bioptic, postmortem or a combination of these criteria. Twelve patients (7% of cases) showed evidence of myocardial disease in ≥ 1 relative; 27 patients with myocardial disease were detected in the 12 families, but a suspected history of myocardial involvement was present in a further 16 cases. In 6 families proband and relatives were affected by DC (total 14 cases); in 1 of these families the disease began with an atrioventricular block. In 4 families the relatives showed the presence of myocarditis at the endomyocardial biopsy. In 2 families the relatives presented a right ventricular cardiomyopathy. The mode of inheritance was autosomal dominant in 7 families, recessive in 4; X-linked pattern may be hypothesized in 1. Nine patients died under the age of 45 years: 2 of sudden death, 6 of chronic heart failure and 1 of cerebral embolism. Familial transmission is not rare. Different modes of genetic transmission (autosomal dominant, recessive and X-linked) and different forms of myocardial disease suggest that familial DC may be a multifactorial disease.

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Dilated cardiomyopathy (DC) is a heart disease of unknown etiology, characterized by depressed ventricular function, usually associated with enlargement of cardiac chambers.¹ It is considered a syndrome, in which several factors (viral, pregnancy and puerperium, alcohol, arterial hypertension, genetic factors, etc.) may have a predisposing or a determinant role.¹ In contrast to hypertrophic cardiomyopathy, in which hereditary mechanisms have been well analyzed,^{2,3} familial factors in DC have been poorly studied until now and are seldom considered. However, recent studies showed that familial forms may be discovered in a variable percentage of patients, ranging from 2 to 50% of cases.⁴⁻⁶ Since 1979 we systematically studied in a prospective manner 165 consecutive patients with a diagnosis of DC. In this group of patients 12 were identified in whom at least 1 member of the family was affected by DC. This study analyzes the characteristics of familial forms of DC with particular focus on prevalence and modalities of inheritance.

METHODS

One hundred sixty-five patients with DC were consecutively and prospectively studied from January 1979 to June 1988. DC was diagnosed if ventriculographic ejection fraction was <0.50 (normal values in our laboratory are 0.67 ± 0.08), in the presence of at least 1 of the following: signs of left- or right-sided cardiac failure, roentgenographic cardiomegaly (cardiothoracic ratio >0.50), electrocardiographic anomalies (conduction abnormalities, severe ventricular arrhythmias or both) or history of embolism, and in the absence of any evident cause of depressed left ventricular function. Exclusion criteria were coronary heart disease, valvular heart disease, arterial hypertension, myocarditis, systemic diseases, congenital heart diseases and cor pulmonale.

In all patients the following baseline evaluations were performed at entry into the study: physical examination, standard and ambulatory electrocardiogram, chest x-ray, M-mode and 2-dimensional echocardiography, hemodynamic, ventriculographic and coronary angiographic study and right or left ventricular endomyocardial biopsy. In 18 cases with clinical diagnosis of DC (without cardiac catheterization), the diagnosis was confirmed at autopsy. Patients admitted into the study were questioned if cases with presumed or confirmed heart disease were present in their families. Patient relatives with suspected myocardial disease underwent clinical, noninvasive and, whenever possible, invasive evaluation. Further information was obtained either from attending physicians or eventually from the hospitals in

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TABLE I Clinical and Pathologic Findings in 27 Patients with Familial Dilated Cardiomyopathy

Family	Sex	Age (yrs)		Clinical Features	ECG Holter	X-ray Cardiomegaly	Echocardiogram LVDD (mm)	LVEF (%)	Histologic Diagnosis	Follow-up (yrs)
		First Symptom	Diagnosis							
A 1*	M	23	30	HF, S ₃	AF, VT, S-AB, LAH	+	60	48	DC	Dead (32)
2	M	22	22	MP	SVT, VEB, VT	0	52	53	Healed myocarditis	Stable (27)
B 1	M	45	45	HF, S ₃ , S ₄ , MR	VEB, LBBB	+	75	24	DC	Stable (51)
2	M	20	21	HF, MR	1°A-VB	+			Active myocarditis	Dead (21)
C 1	M	44	44	S ₃ , MR	VEB, VT	+	83	26	DC	Improved (45)
2	M	33	35	HF, S ₃ , S ₄ , MR	LVH	+	85		DC†	Dead (35)
D 1	F	9	12	—	VEB, VT	0	42		RVC	DC/Abort. SD (16)
2	M	28	29	—	SSS, VEB, LAV	+	54	RVEF = 50 61	Active myocarditis	SD (35)
E 1	F	31	37	HF, S ₃ , S ₄ , MR	AV, VEB, LVH	+	60	49	DC	Stable (44)
2	M	27	37	—	late potentials, VT	0	50	56	RVC	Stable (42)
F 1	F	36	54	HF, S ₃ , S ₄ , MR, TR	VEB, LAH	+	60	29	DC	Dead (58)
2	M	15	20	MR	VEB, VT	0	56		DC	SD (22)
3	M	19	30	S ₄	VEB, VT	0	68	35	DC	HF (36)
G 1	M	68	69	HF, S ₃ , S ₄ , MR	LBBB	+	81	25	DC	Dead (73)
2	F	36	36	MP	VEB, VT	0	47	65	DC	Stable (39)
H 1	M	43	43	HF	AF, VT, 2°–3°A-VB	+			DC†	Dead (44)
2	M	41	41	—	VEB, VT, 2°A-VB	0	60	61	DC	Stable (43)
I 1	M	41	41	HF, MR	VEB	+	61	44	DC	Stable (43)
2	M	44	45	HF, S ₄	T-wave changes	+	75		DC	Dead (45)
L 1	F	5	9	S ₃ , MR	VEB, VT, LAH, Q	+	56	26	DC	Dead (11)
2	F	12	13	—	Q; T-wave changes	+	50	22	—	Stable (16)
M 1	M	30	30	S ₃ , S ₄	VEB, VT, LAH	+	87	17	DC	Stable (31)
2	M	27	27	—	VEB	0	60	52	DC	Stable (28)
3	F	29	33	S ₄ , MR	VEB, VT, LAH	+	71	23	DC	Stable (33)
4	M	37	42	S ₄ , MR	VEB	+	70	47	DC	Stable (47)
N 1	M	12	12	HF, S ₃ , S ₄	VEB, RBBB, LAH	+	58	24	DC	Stable (12)
2	M	16	16	S ₃ , S ₄ , MR, TR	VEB, RBBB, LAH	+	70	19	Healing myocarditis	Dead (16)

* First case—proband; † diagnosis made by another hospital.

AF = atrial fibrillation; A-VB = atrioventricular block; HF = heart failure; LAH = left anterior hemiblock; LBBB = left bundle branch block; LVDD = left ventricular diastolic diameter; LVH = left ventricular hypertrophy; LVEF = left ventricular ejection fraction; MP = mitral prolapse; MR = mitral regurgitation; RBBB = right bundle branch block; RVC = compatible with right ventricular cardiomyopathy; RVEF = right ventricular ejection fraction; Q = Q wave; S-AB = sinoatrial block; SD = sudden death; SSS = sick sinus syndrome; SVT = supraventricular tachycardia; TR = tricuspid regurgitation; VEB = ventricular ectopic beats; VT = ventricular tachycardia.

which they had been admitted. Criteria for the diagnosis of familial DC were the presence of myocardial diseases in ≥ 1 member of the proband's family.

RESULTS

Of the 165 patients with DC, 12 (7%) had ≥ 1 relative affected by familial cardiomyopathy. Data of the 12 families are listed in Table I.

Twenty-seven patients were studied, but a highly suggestive history of myocardial involvement was present in a further 16 cases.

The mean age at diagnosis was 32 years (range 9 to 69) in the group with familial DC (20 men, 7 women), and 47 (range 8 to 70) in the other patients ($p < 0.01$). In 6 families proband and relatives were affected by DC (total 14 cases). In 1 of these families the disease began with an atrioventricular block. In 4 families the relatives' biopsy examinations showed the presence of myocarditis. In 2 families relatives had a right ventricular cardiomyopathy. The pedigrees of the 12 family cases are shown in Figure 1.

Seven families showed an autosomic dominant pattern (A,D,E,F,G,H,I), 4 a recessive pattern (B,L,M,N).

In 1 family an X-linked pattern may be hypothesized (C).

During the follow-up 11 of 27 familial cases died: 8 of heart failure, 2 of sudden death and 1 of cerebral embolism. The mean age at death was 36 years (range 11 to 73) (versus 45 years (range 10 to 74) in the group of nonfamilial DC).

DISCUSSION

The familial occurrence of DC, apparently a rare event, has been poorly studied and its real prevalence is still unknown. Nevertheless, the study of hereditary-familial factors as a possible cause of DC is important because of the potential information to be gained regarding the etiology of DC.⁷

There have been several reports of families with DC, usually considered to be sporadic. Ross et al⁸ analyzed 5 generations of a family with DC, conduction and rhythm disturbances, sudden death and autosomal dominant pattern of transmission. Harveit et al⁹ reported a family with DC transmitted with autosomal dominant pattern in 3 generations. Voss et al¹⁰ described a family in which 4 women (mother and 3 sisters) presented a

genetically transmitted form of peripartum cardiomyopathy: the investigators hypothesized DC aggravated by the hemodynamic or immunologic alterations of pregnancy and puerperium. MacLennan et al¹¹ observed a family with DC, young age of presentation and high incidence of sudden death. The familial occurrence of right ventricular dysplasia (right ventricular cardiomyopathy), characterized by enlarged right ventricle and normal or quite normal left ventricle, has also been reported.¹²⁻¹⁴ Finally, O'Connell et al¹⁵ described the clinical and pathologic findings of myocarditis in 6 of 7 members of 2 families with DC.

Frequency of familial dilated cardiomyopathy: In a study on natural history of DC carried out by Fuster et al,⁴ 2% of patients had a familial disease. This study was, however, retrospective and nonfinalized. Other investigators observed a low frequency: Costanzo-Nordin et al¹⁶ 2%, Lengyel and Kokeny¹⁷ 5%. Two studies conducted with a systematic analysis of the families with DC in Japan demonstrated a frequency of 31%¹⁸ to 52%⁶ of familial forms. Such a wide difference of prevalence is probably related to different methodology of investigation and to different diagnostic criteria. For instance, in the study of Sekiguchi et al¹⁸ the incidence decreased from 31 to 6%, if only cases with highly reliable and conclusive proof of familial pattern are considered.

More recently, Michels et al⁵ studied the incidence of familial cases of DC retrospectively in 169 patients. In this study, mainly based on questionnaires, an incidence of 6% was found. Another recent retrospective study on 184 patients with DC undergoing cardiac transplantation¹⁹ identified a familial etiology in 9% of cases. In children the values ranged from 10%²⁰ to 25%.²¹ Finally, considering patients with "mild" DC, (i.e., DC without significant ventricular dilatation), 4 of 5 had a familial history.²²

In our prospective study of 165 patients with DC, examined between 1979 and 1988, 7% of cases had at least 1 member of the family affected. These data may, however, underestimate the real incidence of the phenomenon: in fact the disease may be latent in some relatives or may not appear in the family history. Furthermore, cases in which it was not possible to obtain an exhaustive documentation of the disease have not been considered.

Mode of inheritance: The mode of inheritance of familial DC was at first considered to be autosomal dominant.²³ Since then, a recessive autosomic allele⁶ or both modes of inheritance⁷⁻¹⁴ have also been described. An X-linked genetic transmission was finally observed.²⁴

In our study 7 of 12 families showed an autosomal dominant inheritance, 3 of 12 a recessive one and in 1

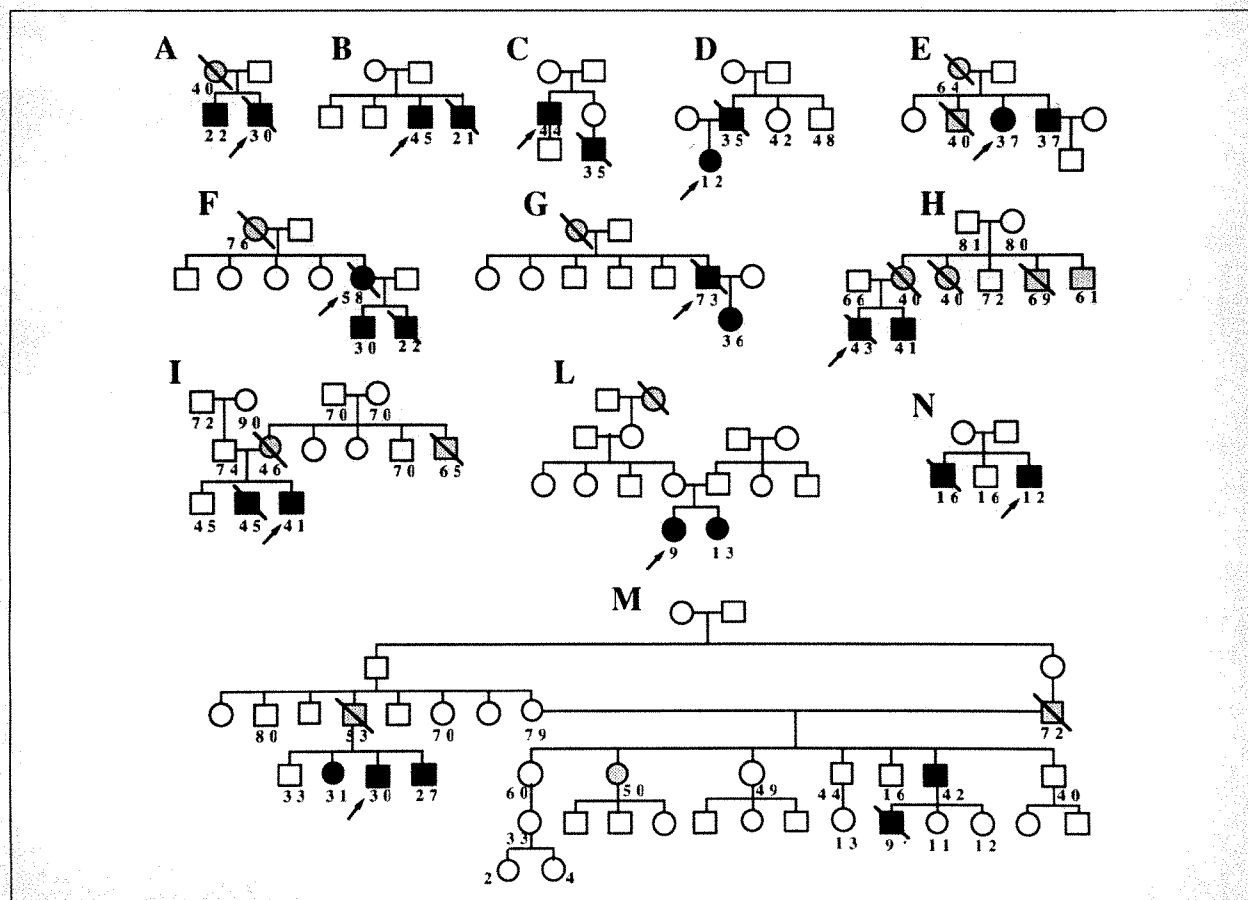


FIGURE 1. Pedigree of 12 families showing mode of inheritance of cardiomyopathy. Numbers give age at presentation or age at death (slashed line). Blackened squares (men) and circles (women) indicate confirmed cases. Hatched lines indicate suspected cases. Arrows indicate probands.

an X-linked transmission may be hypothesized. These data suggest that different genetic factors may be involved, resulting in a common phenotype of myocardial damage.

Clinical features: At the time of diagnosis our patients had a mean age of 32 years, significantly lower than the mean age of cases with nonfamilial DC (47 years, $p < 0.01$). Eleven patients died during follow-up; 3 presented with sudden unexpected death: 1 aborted, while 2 patients died. All 3 patients were under the age of 35, 2 had features of right ventricular cardiomyopathy (with left ventricular involvement) and 1 had DC after myocarditis.

A synthesis of the characteristics of familial forms of DC is listed in Table I. A wide range of clinical and pathologic expressions was present in the family as well as in the same patient, suggesting once more a multifactorial or a pluricausal disease.

Of particular interest is the presence in the same family of DC and myocarditis (families A,B,D). O'Connell et al¹⁵ recently identified an inflammatory pattern in 2 families, in which the affected members presented a clinical picture of DC. An abnormal susceptibility to virus-induced myocarditis or an abnormal immune response determined by genetic background may be hypothesized in such cases.

A second point of interest is the presence of cases with right ventricular cardiomyopathy, with various degrees of left ventricular involvement. Familial forms have been described in "arrhythmogenic right ventricular dysplasia" (right ventricular cardiomyopathy).¹²⁻¹⁴ All of them probably represent various aspects of a spectrum of myocardial disease that involve mostly the right ventricle, but sometimes also involve the left one.²⁵ The pathologic characteristics of these cases are a markedly dilated right ventricle and a progressive replacement of the myocardium by fatty and fibrous tissue.¹⁴ An abnormal development or a progressive atrophy of right ventricular myocardium genetically determined have been hypothesized.

Finally, conduction diseases and DC, as in family H, have been observed also by other investigators^{7,23} in humans and in animal models. Moreover, several descriptions of familial conduction disturbances have also been published.²⁶

The characteristic progression of the disease, with the development of conduction abnormalities, arrhythmias and subsequent heart failure and a typical picture of DC, suggests a peculiar genetic alteration, with a phenotypic expression common to the other types of DC.

Etiologic considerations: Different etiopathogenetic factors of myocardial diseases have been identified in human pathology, as carnitine deficiency,²⁷ or in animals, as the genetically transmitted DC of Syrian hamsters, probably related to an abnormal biosynthesis of the cellular membrane system.²⁸

In familial DC, characterized by conduction defects and heart failure, a depression of calcium-adenosine triphosphatase activity has been demonstrated.⁷ Mitochondrial abnormalities that may be related to bio-

chemical defects have been recently described in familial DC.²⁹

HLA typing, considered as an expression of genetic background, has been evaluated in familial DC. Koike et al,³⁰ analyzing 2 families with DC, observed that a specific HLA antigen could not be identified; however, all the affected individuals shared an identical HLA-haplotype. HLA genes are located in the region of the sixth chromosome, which probably controls some immune mechanisms: a correlation between HLA antigens and alterations of the immunologic system may be supposed.

Several recent studies support the hypothesis that DC and myocarditis may both be related to alterations of immunoregulation.

In the 2 families studied by O'Connell et al¹⁵ probands and the affected relatives had a clinical pattern of DC and active myocarditis based on laboratory data (endomyocardial biopsy and gallium-67 scans). In 1 case it was possible to document a deficiency of suppressor lymphocyte function. This patient improved after immunosuppressive therapy. In these cases a hereditary defect of lymphocytes with resultant predisposition to myocarditis may be hypothesized. Such mechanisms and the subsequent evolution to DC may explain the presence in some families of cases of both myocarditis and DC.

Based on our and other investigators' findings, at least 2 main mechanisms may be expected in the development of familial DC: (1) genetically determined "myopathy," possibly related to biosynthesis alterations (of membrane systems? mitochondria? contractile proteins?); and (2) genetic transmission of predisposing factors, such as altered immunologic system and subsequent abnormal susceptibility to pathogenic agents. Further studies should be undertaken to analyze these hypotheses.

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Influence of Aging on Pulmonary Hemodynamics in a Population Free of Coronary Artery Disease

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Previous studies showing an increase in pulmonary artery (PA) pressures and vascular resistance with aging have not systematically excluded subjects with coronary artery disease or left ventricular systolic dysfunction. To better determine the influence of aging on PA hemodynamics in the absence of disease, we identified 47 normal subjects angiographically free of coronary artery disease (18 men, 29 women) with normal left ventricular systolic function (ejection fraction $\geq 50\%$ and left ventricular end-diastolic pressure < 14 mm Hg) from 5,508 consecutive patients undergoing cardiac catheterization and coronary angiography between September 10, 1982 and March 9, 1987. All subjects met a set of clinical and laboratory criteria identifying them as normal. In group I (age ≥ 60 years) mean PA pressure was 16 ± 3 mm Hg, pulmonary vascular resistance was 124 ± 32 dynes s cm^{-5} and the pulmonary/systemic vascular resistance ratio was 0.099 ± 0.046 . In contrast, in group II (age < 60 years), these values were lower at 12 ± 2 mm Hg, 70 ± 25 dynes s cm^{-5} and 0.057 ± 0.019 , respectively (all p values < 0.01 to 0.001). All these parameters increased linearly with age ($r = 0.69$, $p < 0.001$ for pulmonary vascular resistance). The differences were not attributable to body surface area or gender. There was no difference in cardiac output, PA wedge pressure, aortic pressure or systemic vascular resistance between the 2 groups. Thus, PA pressure and vascular resistance increase with aging, a change not attributable to coronary disease or left ventricular systolic dysfunction.

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There are fewer studies of the pulmonary circulation than of the systemic vasculature due to the relative inaccessibility of the pulmonary vessels. Those performed have shown an increase in pulmonary artery (PA) pressure and vascular resistance with aging.¹⁻⁴ In these studies, coronary artery disease was excluded on clinical or noninvasive grounds; left-sided heart pressures were not measured nor was ventriculography performed. Most of these studies were performed before the era of coronary angiography.¹⁻³

To establish the specific influence of aging on PA hemodynamics, subjects should have coronary artery disease and ventricular dysfunction excluded. Ethical constraints preclude prospective coronary angiographic evaluation of a large number of normal subjects. Therefore, we undertook a retrospective study to define the influence of aging on the pulmonary vasculature in a population with angiographically defined coronary anatomy and ventricular function.

METHODS

Each subject was included after evaluation of his or her medical record and cardiac catheterization data. All were ≥ 20 years of age and were identified from 5,508 consecutive cardiac catheterizations performed in the Division of Cardiology, University Hospital, Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine from September 10, 1982, to March 9, 1987. The subjects were divided into the following 2 groups: group I was made up of subjects ≥ 60 years of age and group II was made up of subjects ≥ 20 but < 60 years. All subjects with a final diagnosis of "normal" (no abnormalities found) were reviewed.

Using the hospital record, the subjects' medical history and physical examination at the time of cardiac catheterization were evaluated to exclude those with evidence of cardiac and/or pulmonary disease. The chest x-ray report was reviewed for clear lung fields, normal heart size and no evidence of active cardiac and/or pulmonary disease. Subjects with isolated pulmonary granulomata were not excluded from the study. Chest x-rays were reviewed by an investigator (WRD) if the report was unclear. The electrocardiogram was reviewed and subjects were excluded for rhythm disturbances and evidence for ischemia, infarction or hypertrophy. Those with a clinical history of systemic hypertension (by history in medical record, requiring drug therapy or blood pressures on the wards > 140 mm Hg systolic or > 90 mm Hg diastolic) were excluded. Those with abnormal pulmonary function tests (when performed) were excluded. A history of tobacco use without a history of

TABLE I Systemic Hemodynamics and Blood Gas Results

Dependent Variable	Group I (n = 14)		Group II (n = 33)	
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
Age (yrs)	64 $\pm$ 3	60 to 69	42 $\pm$ 8	24 to 55
Body surface area (m ²)	1.77 $\pm$ 0.17	1.40 to 2.12	1.84 $\pm$ 0.23	1.37 to 2.30
Cardiac output (liters/min)	5.6 $\pm$ 1.4	4.0 to 8.3	6.3 $\pm$ 1.5	3.4 to 9.9
Cardiac index (liters/min/m ²)	3.2 $\pm$ 0.9	2.2 to 5.4	3.4 $\pm$ 0.7	2.2 to 5.3
Ejection fraction	69 $\pm$ 12	48 to 93	64 $\pm$ 09	49 to 83
Heart rate (beats/min)	79 $\pm$ 16	50 to 120	77 $\pm$ 13	48 to 112
LVEDP (mm Hg)	8 $\pm$ 3	5 to 13	9 $\pm$ 3	4 to 13
O ₂ sat. (%)	97 $\pm$ 2	94 to 100	97 $\pm$ 2	91 to 100
Pa O ₂ (mm Hg)	81 $\pm$ 14	71 to 108	84 $\pm$ 8	71 to 100
PCWP (mm Hg)	7 $\pm$ 3	3 to 13	7 $\pm$ 3	2 to 13
Mean RAP (mm Hg)	4 $\pm$ 2	1 to 6	4 $\pm$ 2	1 to 8
Systolic SAP (mm Hg)	133 $\pm$ 18	110 to 180	128 $\pm$ 17	100 to 160
Diastolic SAP (mm Hg)	69 $\pm$ 9	60 to 90	75 $\pm$ 11	50 to 100
Mean SAP (mm Hg)	94 $\pm$ 13	72 to 125	97 $\pm$ 10	75 to 115
SVR (dynes s cm ⁻⁵)	1355 $\pm$ 342	704 to 1820	1252 $\pm$ 363	711 to 2612
SVRI (dynes cm ⁻⁵ m ²)	2439 $\pm$ 717	1304 to 3757	2296 $\pm$ 569	1208 to 4440

There were no significant differences between the groups for any variable listed other than age.

LVEDP = left ventricular end-diastolic pressure; O₂ sat = arterial oxygen saturation; PA O₂ = arterial partial pressure of oxygen; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SAP = systemic arterial pressure; SD = standard deviation; SVR = systemic vascular resistance; SVRI = systemic vascular resistance index.

TABLE II Pulmonary Artery Pressure and Vascular Resistance

	Group I (n = 14)		Group II (n = 33)	
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
PA systolic (mm Hg)	26 $\pm$ 5*	16 to 35	20 $\pm$ 4	13 to 28
PA diastolic (mm Hg)	11 $\pm$ 3*	8 to 18	9 $\pm$ 2	6 to 14
Mean PA (mm Hg)	16 $\pm$ 3*	11 to 23	12 $\pm$ 2	8 to 19
Mean PA-PCWP (mm Hg)	9 $\pm$ 3†	5 to 16	5 $\pm$ 2	1 to 8
PVR (dynes s cm ⁻⁵)	124 $\pm$ 32†	75 to 178	70 $\pm$ 25	12 to 112
PVRI (dynes s cm ⁻⁵ m ²)	225 $\pm$ 69†	133 to 337	128 $\pm$ 41	24 to 193
PVR/SVR $\times$ 1000	99 $\pm$ 46†	50 to 242	57 $\pm$ 19	12 to 95

* p < 0.01 versus group II; † p < 0.001 versus group II.

PA = pulmonary artery; mean PA-PCWP = pressure decrease across pulmonary vascular bed; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; PVR/SVR = pulmonary/systemic vascular resistance ratio.

pulmonary disease did not exclude subjects from the study. The subjects were categorized as nonsmokers, ex-smokers and current smokers of <1 pack/day or >1 pack/day.

All subjects underwent right- and left-sided heart catheterization with coronary arteriography and left ventriculography. A variety of fluid-filled catheters were used. Transducers are balanced routinely before each case and rechecked periodically before pressure recording in our laboratory. Each subject's cardiac pressure tracings were reviewed. PA and other pressure values are reported as an average over the respiratory cycle. Hemodynamic inclusion criteria were the following: cardiac index $\geq$ 2.2 liters/min; left ventricular end-diastolic pressure $\leq$ 13 mm Hg; mean right atrial pressure $\leq$ 8 mm Hg; and a mean PA wedge pressure $\leq$ 13 mm Hg. Pressure decrease across the pulmonary vascular bed was calculated as PA mean - PA wedge pressure. Systemic and pulmonary vascular resistances (both measured in dynes s cm⁻⁵), systemic and pulmonary vascular resistance indexes (normalized by multiplying resistance values by the body surface area) and the ratio of pulmonary to systemic vascular resistance were calculated from the hemodynamic data.⁵ Cases with poor quality hemodynamic tracings were excluded. Patients

with any occlusive or nonocclusive coronary disease were excluded. Patients with mitral regurgitation, mitral valve prolapse, ejection fraction <50% or regional wall motion abnormalities on ventriculography were excluded.

The following were abstracted from the cardiac catheterization and medical records of each subject: age; gender; height; weight; body surface area; aortic mean, systolic and diastolic pressure; systemic arterial partial pressure of oxygen; arterial oxygen saturation; heart rate; cardiac output and index; and ventriculographic ejection fraction. All study population subjects had an arterial oxygen tension >70 mm Hg and an arterial oxygen saturation >90% at catheterization. The arterial oxygen saturation and oxygen tension determinations were performed with a Corning 168 pH blood gas system (Corning Medical) which was calibrated daily and used throughout the study.

The data were expressed as the mean $\pm$ standard deviation. An unpaired Student's *t* test was used to compare means of the study groups and to examine gender differences. Univariate and multivariate linear regression analysis was used to evaluate the relation between age and the pulmonary variables. Data analysis was conducted on a MacIntosh Plus computer using the

statistical package, Statworks (Data Metrics). A p value <0.05 was accepted as statistically significant.

RESULTS

Forty-seven adults (29 women, 18 men) aged 24 to 69 years (mean 48 ± 13) were identified (Table I). The gender distribution did not differ between groups by chi-square analysis. Most had undergone coronary angiography for chest pain and/or suspected coronary disease. The study group comprised $<1\%$ of the 5,508 cardiac catheterizations performed during the time period in which subjects were identified. This is less than the 5 to 10% of the general population who present with angina and are found to have normal coronary arteries⁶ and reflects the rigorous exclusion criteria used. Twenty-three of the 47 study subjects underwent Ergonovine testing. Results in all 23 subjects were negative. The systemic hemodynamic characteristics of group I and group II did not differ (Table I). Cardiac output was slightly lower in the older group but this was not statistically different. Systemic vascular resistance showed a very weak tendency to increase with age ($y = 905 + 7.8x$, $r = 0.28$, $p < 0.07$).

Group I had higher pulmonary artery pressures (systolic, diastolic and mean) than group II (Table II). Mean pulmonary artery pressure (Figure 1) increased significantly with age. The pulmonary vascular resistance (Figure 2) and the pulmonary/systemic resistance ratio (Figure 3) also increased significantly ($p < 0.001$) with age. The pressure decrease across the pulmonary vascular bed increased with age ($y = 1.1 + 0.1x$, $r = 0.52$, $p < 0.01$) and accounted for most of the age-related change in pulmonary vascular resistance. Pulmonary vascular resistance was inversely related to body surface

area ($r = 0.35$, $p < 0.02$) but this did not explain the variability due to age as the pulmonary vascular resistance index also increased significantly with age ($r = 0.68$, $p < 0.001$). Age accounted for 46% of the variability in the pulmonary vascular resistance index. In multivariate regression analysis, both age and body surface area contributed to the value of pulmonary vascular resistance ($r = 0.74$, $p < 0.001$). Pulmonary vascular resistance was most closely correlated with age ($r = 0.69$, $p < 0.001$, Figure 2). No pulmonary vascular variable differed between men and women.

Nineteen subjects (2 group I, 17 group II) had smoked at one time. Six subjects smoked ≥ 1 pack/day, 6 subjects smoked <1 pack/day and 7 subjects were ex-smokers. None of the pulmonary variables measured in the study were found to be significantly different among the smokers and nonsmokers.

DISCUSSION

This is the first study to document an increase in pulmonary vascular resistance and PA pressure with aging in a group of subjects in which coronary artery disease and left ventricular systolic dysfunction were excluded systematically. This increase was most striking for pressure decrease across the pulmonary vascular bed and indexes derived from it, which were pulmonary vascular resistance and resistance index and the pulmonary/systemic vascular resistance ratio. It was less strong for mean PA pressure. The smaller increase in mean PA pressure with age can be explained in part by the tendency for cardiac output to be lower in our older subjects, a finding described by some^{7,8} but not others.⁹ The increase in pressure and resistance with aging appeared continuous and linear without an apparent

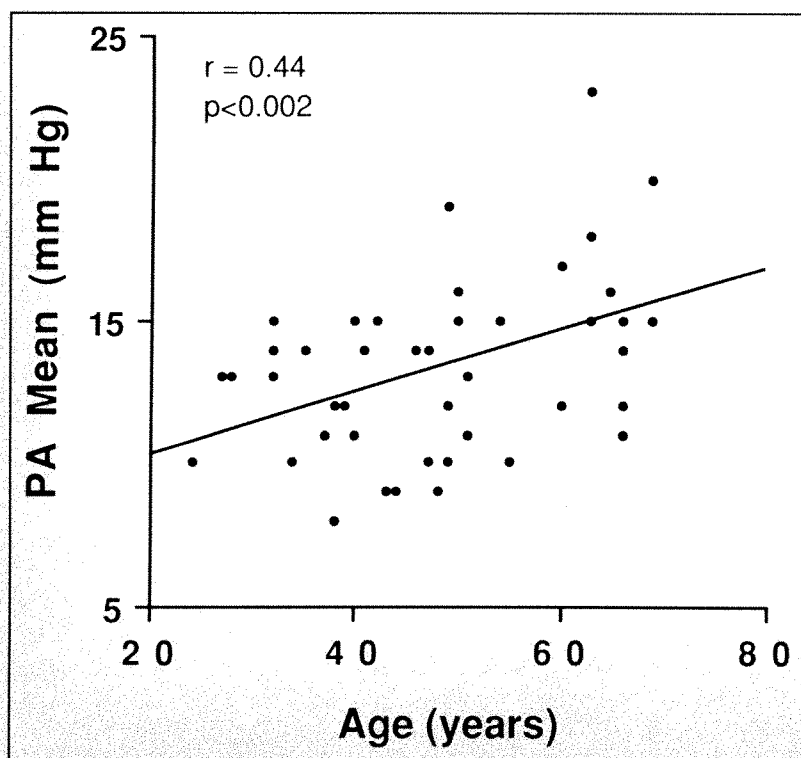


FIGURE 1. Relation of mean pulmonary artery pressure to age in 47 normal subjects. $y = 0.12x + 8$. PA = pulmonary artery pressure.

"breakpoint," as was suggested by Ehrlam⁴ (Figures 1, 2 and 3).

Previous studies examining the influence of aging on pulmonary hemodynamics occurred before the era of modern stress testing or coronary arteriography. One third of Granath's subjects had ST changes with exer-

tion and many had electrocardiographic abnormalities at rest.^{1,10} Other studies used clinical criteria, stress testing or the resting electrocardiogram to screen for coronary disease.²⁻⁴ However, with the high prevalence of coronary disease in an older population, false negative exercise tests are more likely. In 1 study,⁴ most of

FIGURE 2. Relation of pulmonary vascular resistance to increasing age in 47 normal subjects. $y = 11 + 2.02x$. PVR = pulmonary vascular resistance; metric units are dynes cm^{-5} .

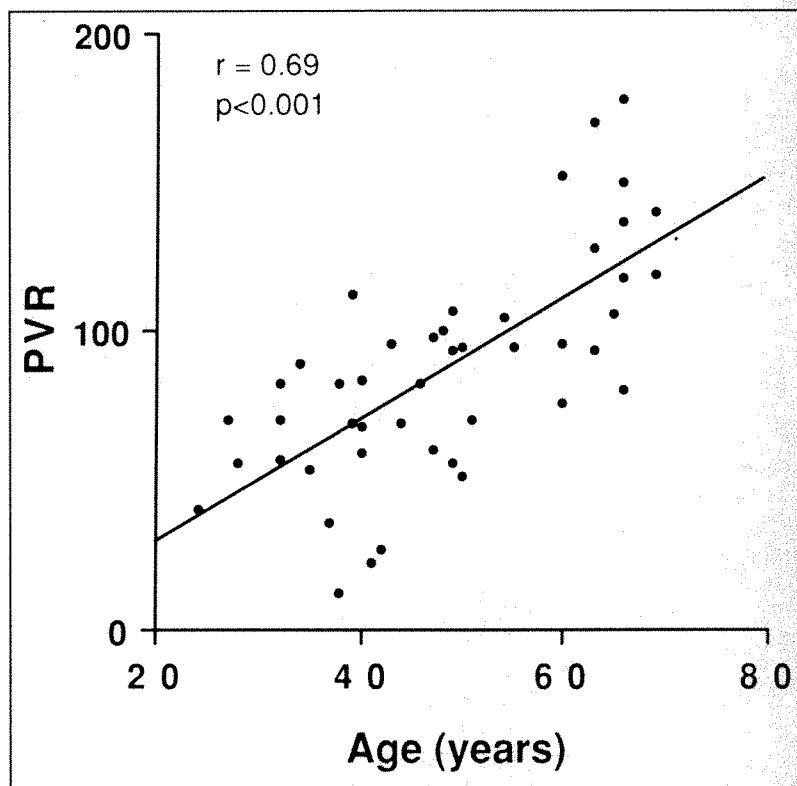
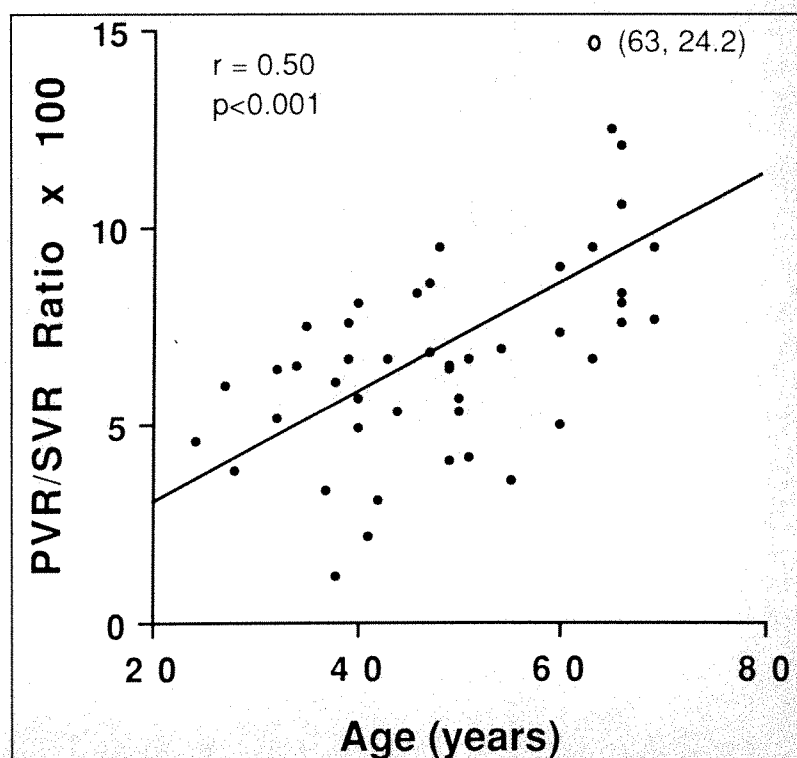


FIGURE 3. Relation of pulmonary/systemic vascular resistance ratio to age in 47 normal subjects. $y = 0.0014x + 0.0027$. PVR/SVR = pulmonary-systemic vascular resistance ratio.



the older subjects had undergone study for suspected pulmonary disease which raises other questions about the true "normality" of their subjects.

The increase in coronary disease prevalence with aging¹¹ and the frequently silent nature of coronary artery disease are well known.^{12,13} In the elderly, the clinical incidence of coronary disease greatly underestimates the incidence of coronary atherosclerosis at autopsy.^{10,14} Doppler studies have documented the increasing frequency of mitral insufficiency with aging, which is frequently not clinically apparent.¹⁵ Because of our study design, clinically inapparent abnormalities of all these factors have been excluded as the cause of our findings. Fortuitously, 49% of the subjects also had an ergonovine challenge and all results were negative.

Several mechanisms could explain the influence of age on pulmonary hemodynamics. A primary abnormality of the pulmonary vascular bed is likely as changes in the systemic circulation with aging are well described.^{7,16-17} Such changes might influence the pulmonary circuit as well. Histopathologic changes in the pulmonary vasculature with aging are also well described.¹⁸⁻²⁰ However, the ratio of pulmonary to systemic vascular resistance also increased with age, suggesting that the effects of aging were proportionately greater in the pulmonary than in the systemic vascular bed. Left ventricular diastolic dysfunction may be responsible for the greater increase in the pulmonary bed as the wedge pressure increases more in older than younger subjects with exercise.^{1,4,21} Abnormalities of left ventricular filling and compliance and increased wall thickness are reported with aging.²²⁻²⁴ Higher systemic afterload may also cause higher pulmonary pressures with aging. However, in the current study, arterial pressure and systemic vascular resistance did not increase with aging.

Limitations: A retrospective study limits the ability to control the quality of collected data or to obtain exercise pulmonary pressures. This was addressed by using stringent exclusion criteria. By this design, many clinically "normal" older subjects were excluded, thus we may have underestimated the degree of change in the pulmonary vascular bed associated with the aging process or the influence of ventricular diastolic function. Our younger subjects had hemodynamic findings similar to published normal subjects.^{5,25-27} The identified trends with aging conform to published findings. Thus, a patient group was identified similar to those of previous studies.¹⁻⁴ Whether the observed changes continue further beyond the age of 70 cannot be addressed as our oldest patient was 69 years of age. Smokers were not excluded; however, smoking has not been found to be associated with the vascular intimal changes seen in the pulmonary circuit with aging in the absence of clinical pulmonary disease.¹⁸

Clinical implications: There is a recognized need for better information concerning normal pulmonary hemodynamics and their relation to age.²⁷ Pulmonary pressures are commonly used as an indicator of the severity

of pulmonary and left-sided heart disease. Our results suggest that using such an approach in older subjects may overestimate the clinical severity of these disorders.

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Prognostic Value of Intravenous Dipyridamole Thallium Imaging in Patients with Diabetes Mellitus Considered for Renal Transplantation

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Patients with diabetes and end-stage renal failure are known to have a high risk for cardiac morbidity and mortality associated with renal transplantation. The most efficient method to determine preoperative cardiac risk has not been established. To determine the effectiveness of intravenous dipyridamole thallium imaging in predicting cardiac events, 40 diabetic renal transplant candidates were studied preoperatively in a prospective trial.

The study group consisted of 40 patients whose average age was 42 years (range 27 to 64); 34 (85%) were hypertensive and 21 (53%) were cigarette smokers. Cardiac history included chest pain in 6 patients and prior myocardial infarction in 3 patients. Dipyridamole thallium imaging showed reversible defects in 9 patients, fixed defects in 8 patients and normal scans in 23 patients. Dipyridamole thallium imaging was performed using 0.56 mg/kg of dipyridamole infused intravenously over 4 minutes.

Cardiac events occurred only in patients with reversible thallium defects, of which there were 6. Of these 6 patients, 3 had cardiac events before transplantation and 3 had them in the early postoperative phase (within 6 weeks of surgery). Of 21 patients who underwent renal transplantation, 3 had cardiac events within 6 weeks of transplantation. The average duration of follow-up was 11 months (range 1 to 21). Thus, dipyridamole thallium imaging is an effective method of identifying renal transplant candidates likely to develop cardiac complications. Routine coronary angiography may not be necessary to screen all renal transplant candidates for coronary artery disease before surgery.

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Coronary artery disease is a major cause of morbidity and mortality in diabetic patients who undergo renal transplantation, with as many as 50% of deaths after transplantation due to cardiac causes.¹⁻⁵ Diabetic patients with end-stage renal disease are increasingly considered as candidates for renal transplantation and a reliable noninvasive method to identify the diabetic patient at risk for ischemic cardiac events is needed.

In previous reports, preoperative cardiac risk assessment with cardiac catheterization or exercise thallium imaging to detect patients with occult coronary artery disease has been evaluated.⁶⁻¹⁰ Cardiac catheterization is the most effective method to identify obstructive coronary disease, but as a screening test, it is relatively expensive. Preoperative exercise thallium imaging is limited by the inability of many diabetic patients to perform the levels of exercise necessary to test cardiac reserve.

Intravenous dipyridamole thallium imaging is a safe and effective procedure that has proven useful in evaluating patients before peripheral vascular surgery and to evaluate postmyocardial infarction risk in patients unable to exercise.¹¹⁻¹⁸ This study prospectively evaluates the prognostic value of dipyridamole thallium imaging in determining preoperative and postoperative cardiac events in a consecutive diabetic patient series considered for renal transplantation.

METHODS

The study population consisted of 40 patients with insulin-dependent diabetes and end-stage renal failure awaiting transplantation (Table I). All patients underwent intravenous dipyridamole thallium imaging at St. Louis University between August 1986 and April 1988. The average age of the patients was 42 (range 27 to 64) years and there were 21 men and 19 women. All patients had insulin-dependent diabetes mellitus. The average duration of diabetes was 20 ± 6 years and 37 patients were diabetic for 15 years or longer. Of the 40 patients, 34 were hypertensive and 21 were cigarette smokers at the time of testing. The intravenous dipyridamole thallium study was conducted on 14 patients before starting dialysis and on 26 patients receiving hemodialysis.

Among the 40 patients in this series, 32 had no history of chest pain or myocardial infarction. Of the 8 remaining patients, 3 had a previous myocardial infarction and 6 had reported chest pain.

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TABLE I Patient Characteristics

	Cardiac Events	No Cardiac Events	Total	p Value
Clinical characteristics				
No. patients	6	34	40	NS
Age (yrs) (x ± SD)	43 ± 10	37 ± 6	42 ± 9	NS
Men	5	16	21	NS
Smoking	4	17	21	NS
Systemic hypertension	4	30	34	NS
Diabetes mellitus (yrs) (x ± SD)	21 ± 5	20 ± 7	20 ± 6	NS
Dialysis (months) (x ± SD)	3 ± 2	12 ± 11	11 ± 10	NS
History of chest pain	3	3	6	NS
History of myocardial infarction	0	3	3	NS

NS = not significant; SD = standard deviation.

Renal transplantation was performed in 21 patients using either living related donors (1 patient), cadaver renal transplants (11 patients) or cadaver renal and pancreas transplants (9 patients) at St. Louis University Hospital or John Cochran Veterans Administration Hospital by the same investigator (PJG).

Dipyridamole thallium imaging: Dipyridamole thallium imaging was performed using 0.56 mg/kg of dipyridamole infused intravenously in a dilute solution over 4 minutes followed by 6 minutes of passive leg swinging at the bedside. After 4 minutes, 2.0 mCi of thallium-201 was injected intravenously. The patients were imaged in 3 views (anterior, 45° left anterior oblique and left lateral) starting 6 to 10 minutes after the completion of the dipyridamole infusion. Delayed images were obtained 4 hours after the immediate images. All images were processed and filmed on 8 × 10 inch x-ray film. The thallium images were reviewed by the same experienced investigator (BRC), blinded to the clinical information. Each of the 3 images was divided into 5 segments and each segment was scored individually for the presence or absence of a thallium defect.¹⁸ The segments were coded as showing normal thallium uptake, slightly reduced uptake or severely reduced uptake. In addition, the redistribution images were compared to those obtained after the dipyridamole infusion and coded as showing no change, or as showing a reversible thallium defect.

The patient's medical history, cardiac catheterization reports, operative report and autopsy data (when performed) were reviewed to document atherosclerotic cardiac risk factors and to document cardiac events and causes of death. A cardiac event was defined as follows: sudden death; myocardial infarction documented by serial electrocardiographic or enzymatic changes; and unstable angina accompanied by typical electrocardiographic changes. Follow-up information was obtained directly from the patient, when possible, and from hospital records.

Statistical analysis: The paired *t* test was used to compare heart rate and systolic blood pressure measurements before and after dipyridamole infusion. Chi-

square analysis or Fisher's exact test was used for comparison of proportions. Continuous variables are presented as the mean ± 1 standard deviation. A *p* value <0.05 was considered statistically significant.

RESULTS

Dipyridamole thallium results: The dipyridamole infusion resulted in a decrease in systolic blood pressure of 21 ± 21 mm Hg (*p* <0.001) and an increase in heart rate of 11 ± 9 beats/min (*p* <0.001). Side effects were reported by 12 (30%) patients. All side effects were mild. Chest pain was induced by dipyridamole in 8 (20%) patients (Table II). Intravenous aminophylline was administered to relieve chest pain in 1 patient and to relieve headache in 3 patients. Of the 40 patients, 23 (56%) had a normal thallium scan immediately and 4 hours after the dipyridamole infusion, 8 had fixed defects and 9 patients had reversible thallium defects (Figure 1).

Follow-up: During the observation phase, 6 patients had cardiac events; 3 events occurred in the preoperative phase and 3 occurred after transplantation, resulting in a total of 2 deaths. All cardiac events occurred in patients with reversible defects on dipyridamole thallium scanning. In addition, 3 patients died of noncardiac causes; 1 patient died preoperatively of hyperkalemia and 2 died postoperatively (1 patient died of sepsis and 1 patient died of hepatic failure). None of the 3 patients with noncardiac deaths had reversible defects on dipyridamole thallium scans.

Preoperative events: While awaiting renal transplantation, 3 patients sustained cardiac events. The cardiac events occurred an average of 3 months (range 1 to 6) after the intravenous dipyridamole thallium test. Cardiac events occurred only in patients with reversible thallium defects; 1 patient had sudden cardiac death and 2 patients had a myocardial infarct determined by serial electrocardiographic and enzymatic changes. One additional patient died in the preoperative period due to noncardiac causes, including hyperkalemia and other metabolic derangements. At the time of this report, the 17 surviving patients are awaiting renal transplantation, including both patients who had myocardial infarctions. There were no cardiac events among the patients who had normal scans or fixed thallium defects (Table II). The average follow-up interval was 11 months (range 1 to 21).

Postoperative events: Twenty-one patients have had renal transplantation. Cadaver renal transplants were performed in 11 patients, combined renal and pancreas cadaver transplants were performed in 9 patients and 1 patient received a living related donor renal transplant. The renal transplant procedures were performed 7 months (range 1 to 9) after the dipyridamole thallium test.

Cardiac events occurred in 2 patients within 10 days after surgery. One patient died suddenly and 1 patient had unstable angina requiring intensive medical therapy. Both patients had an abnormal thallium scan before transplantation (both patients had a reversible defect).

In the late postoperative period (>10 days postoperatively) 1 patient had a small myocardial infarction; this patient had a reversible thallium defect at the time of dipyridamole thallium imaging. Of the 11 transplanted patients who had a normal scan, none had a cardiac event in the postoperative period, although 2 patients died of noncardiac causes (hepatic failure, sepsis).

Cardiac catheterization: Of the 9 patients with reversible defects, 8 had cardiac catheterization done either preoperatively or postoperatively. Catheterization was not performed in 1 asymptomatic patient with a reversible defect because the patient died suddenly before the test was scheduled. Of the 8 patients with reversible defects and catheterization, 5 had ≥ 1 major artery with $\geq 70\%$ stenosis. Of the 5 patients, myocardial infarction occurred in 2 before transplant. Both patients had cardiac catheterization after their infarction and had occluded infarct-related vessels. Revascularization was not attempted. Catheterization was performed preoperatively in 2 patients to investigate their reversible defects. A coronary angioplasty was performed for 1 patient who subsequently received a transplant. The patient died suddenly in the early postoperative period. The other patient had diffuse coronary artery narrowings $\geq 70\%$ in the 3 major arteries, but no symptoms of ischemia. This patient received a transplant without preoperative revascularization and had unstable angina postoperatively, but no myocardial infarction. The fifth patient had a small reversible defect on thallium scanning and no symptoms of cardiac ischemia. Cardiac catheterization was not performed before transplant. After transplant (5 weeks), the patient had a myocardial infarction and had a cardiac catheterization and angioplasty with good results. No significant stenoses were present in 3 patients with reversible defects on thallium scanning. All of these patients were women and the thallium scans were suggestive of possible breast attenuation artifact.

TABLE II Test Results

	Cardiac Events (n = 6)	No Cardiac Events (n = 34)	Total	p Value
Dipyridamole test characteristics				
Chest pain with dipyridamole	3	5	8	NS
ECG changes with dipyridamole	3	0	3	<0.001
Reversible thallium defects	6	3	9	<0.001
Fixed thallium defects	0	8	8	NS
No thallium defects	0	23	23	<0.01

ECG = electrocardiographic; NS = not significant.

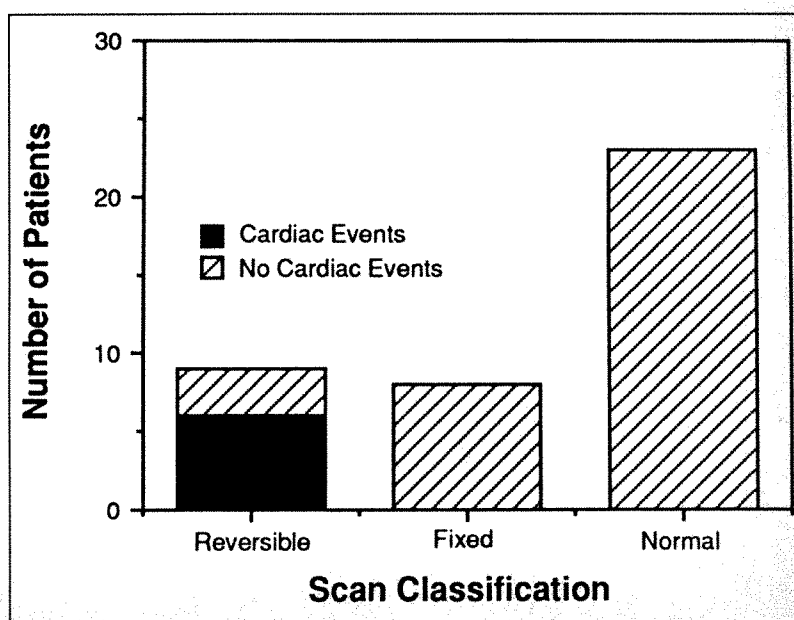
DISCUSSION

Patients with long-standing diabetes and renal failure represent a clinical patient cohort at high risk for coronary artery disease. Thus, routine screening for coronary artery disease before renal transplantation is considered standard medical care. A careful history and physical examination preoperatively in this patient subgroup is not sufficiently sensitive to detect patients with occult coronary disease. In our patient series, 3 of the 6 patients who had a cardiac event were asymptomatic at the time of evaluation before transplantation.

Diabetic patients with renal failure frequently have other associated atherosclerotic risk factors, such as hypertension, which was present in 85% of our patients. Hypercholesterolemia and hypertriglyceridemia have been reported in renal dialysis patients and may further increase the risk for atherosclerosis.^{19,20} In patients with occult coronary disease, tolerance of episodes of myocardial ischemia may be decreased due to the concomitant anemia associated with chronic renal failure.³

Braun reported a 25% incidence of obstructive coronary artery disease ($\geq 70\%$ narrowings) in 100 patients with diabetes and renal failure who underwent cardiac catheterization before renal transplantation.²¹ Other au-

FIGURE 1. Among 40 diabetic patients undergoing evaluation for renal transplantation, preoperative and postoperative cardiac events occurred only in those with reversible defects on dipyridamole thallium testing.



thors have also reported on the angiographic findings in diabetics awaiting transplantation and have proposed cardiac catheterization as a routine preoperative screening test for transplant candidates.^{22,23} Routine cardiac catheterization, however, is costly and exposes the patients with marginal renal function to radiographic contrast material which may further damage the kidneys and result in the need for chronic hemodialysis.²⁴

Exercise thallium imaging is also reported to be a useful preoperative screening test for coronary disease in diabetics awaiting renal transplantation. Philipson et al⁸ reported 60 patients who underwent exercise thallium imaging before renal transplantation. None of the 7 patients who had a normal thallium test had a cardiac event. However, the study was limited by the fact that only 12 patients (20% of the patient series) were able to perform adequate levels of exercise stress to test cardiac reserve. Morrow et al⁹ reported only 6 of 85 patients screened with exercise testing before transplantation were able to reach 85% of their age-predicted maximum heart rate. Clearly, the inability to adequately exercise and test cardiac reserve in diabetics with chronic renal failure limits the usefulness of exercise thallium imaging as a preoperative screening procedure.

We began using dipyridamole thallium imaging as a noninvasive alternative to routine stress thallium testing because many of our patients were unable to perform treadmill exercise. Previous reports have shown that dipyridamole thallium imaging is very sensitive for the detection of coronary artery stenoses.²⁵ Dipyridamole is cleared primarily through biliary excretion²⁶ and thallium kinetics during the testing interval are not believed to be influenced by renal clearance. Based on our results in 40 patients, we believe that dipyridamole thallium imaging is a helpful screening test for assessing preoperative cardiac risk in diabetic patients with renal failure awaiting transplantation. None of the 23 patients with normal scans had a cardiac event in the preoperative or postoperative periods. We also found that thallium defects which we originally described as minor were of diagnostic significance in this population. Of 5 patients with a small reversible defect, 3 had a cardiac event. In our series, 6 of the 9 patients with reversible defects had cardiac events. None of our patients with fixed defects had a cardiac event.

Among the 6 patients with reversible defects, 3 had cardiac events before transplant surgery and 3 after transplant surgery. The dipyridamole thallium scan was an effective predictor of cardiac morbidity and mortality in this high-risk patient group, even in patients awaiting surgery. In patients with reversible ischemia who had transplants, 3 cardiac events were observed despite intensive therapy, including preoperative coronary angioplasty in 1 patient. Brown et al²⁷ studied 36 uremic diabetic candidates and 29 nondiabetic candidates for renal allograft surgery, risk-stratifying the patients using dipyridamole thallium imaging and radionuclide ventriculography. In this series, there were 16 deaths, 6 of which were cardiac. After a mean follow-up of 23 months, no patient had a nonfatal myocardial infarction and there were no perioperative cardiac events in the 35

patients who received renal allografts. Each of the 3 patients who had a reversible thallium defect died of cardiac causes compared to only 3 of the 62 remaining patients who did not have a transient thallium defect. Our data confirm the usefulness of intravenous dipyridamole thallium imaging in this clinical patient subset.

Although the number of patients we studied is limited, our results suggest the following: optimal interpretation of the intravenous dipyridamole thallium test in this clinical patient subset should include reading borderline defects as abnormal to optimize sensitivity, recognizing that this will decrease specificity somewhat; and patients with a reversible dipyridamole thallium defect should have preoperative cardiac catheterization to evaluate coronary artery disease extent.

This study is limited by the fact that we did not perform routine electrocardiography and cardiac enzyme determinations in the postoperative period. Only patients with symptoms that suggested cardiac ischemia were tested as a part of their normal postoperative care. It is possible that we have underestimated the incidence of postoperative myocardial ischemia by not performing electrocardiograms and enzyme determinations on all patients. One further limitation is that intravenous dipyridamole is an investigational drug.

We conclude that intravenous dipyridamole thallium imaging is a safe noninvasive technique which can be used to screen all patients with diabetes and renal failure awaiting renal transplantation. Based on the results of the test, patients can be stratified for preoperative cardiac risk and many can have a safe transplant without having cardiac catheterization.

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Superior Vena Cava Doppler Flow Velocity Patterns in Pericardial Disease

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Doppler superior vena cava (SVC) flow patterns were studied in 34 patients with pericardial disease and in 8 normal adults; the pulse transducer on the echocardiographic instrument was used for respiratory monitoring, rather than a separate nasal thermistor-based device. First expiratory SVC diastolic flow velocities (D_{fe}) did not differ in normal subjects and patients with hemodynamically insignificant pericardial effusions (23 ± 3 cm/s and 29 ± 13 cm/s, difference not significant). D_{fe} were <15 cm/s only in the 14 patients with cardiac tamponade (9 ± 3 cm/s, $p < 0.01$). A ratio of systolic to diastolic flow velocity ≤ 1.1 in the first expiratory beat distinguished constrictive pericarditis from all other groups ($p < 0.01$), although not from restrictive cardiomyopathy. Expiratory ablation of diastolic SVC flow mimicking cardiac tamponade was not observed in constrictive pericarditis. Respiratory variation in SVC flow velocities was slight in normal subjects and patients with constrictive pericarditis, increased in patients with hemodynamically insignificant pericardial effusions ($p < 0.01$) and greatest in patients with cardiac tamponade ($p < 0.01$). Quantitative analysis of SVC flow velocity patterns is a useful addition to the echocardiographic evaluation of pericardial disease.

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The abnormalities in systemic venous return that accompany cardiac tamponade and constrictive pericarditis were initially described from bedside examination of the jugular veins. Invasive studies with electromagnetic and Doppler flow probes have shown that in cardiac tamponade, diastolic venous return is diminished or absent, while in rigid constrictive pericarditis, early diastolic venous return is augmented.^{1,2} Doppler ultrasound of the superior vena cava (SVC) provides a clinically useful, noninvasive method to assess the patterns of systemic venous return in patients with pericardial disease.^{3,4} In this study, SVC Doppler was used to show abnormal flow velocity patterns that distinguished patients with cardiac tamponade and constrictive pericarditis from normal subjects and patients with hemodynamically insignificant pericardial effusions.

METHODS

Study population: Echocardiograms and SVC Doppler studies were performed in 8 normal subjects and 34 patients presenting to Vanderbilt University Hospital with pericardial disease over 20 months. Although not required for this study, sinus rhythm was present in all patients at the time of Doppler examination. No patient had more than mild tricuspid regurgitation by pulsed wave Doppler examination before the SVC study.

The subjects were divided into 4 groups. Group I consisted of 8 normal subjects without evidence of cardiopulmonary disease by history, physical exam or echocardiography. Group II consisted of 17 patients with cardiac tamponade. Three of these patients had Doppler studies inadequate for interpretation and were excluded from further analysis. Cardiac tamponade was diagnosed clinically when a pericardial effusion was associated with increased jugular venous pressure and either pulsus paradoxus >10 mm Hg or systemic hypotension (systolic blood pressure <100 mm Hg). Elevation and equalization of intracardiac diastolic pressures within 5 mm Hg was documented in the 10 patients with cardiac tamponade who underwent cardiac catheterization. Two patients with cardiac tamponade had constrictive physiology documented after pericardiocentesis in the catheterization laboratory. These 2 patients with effusive-constrictive pericarditis were only included in group II during data analysis. Group III consisted of 10 patients with moderate or large circumferential pericardial effusions by 2-dimensional echocardiography and no clinical signs of cardiac tamponade. Group IV consisted of 7 patients with constrictive pericarditis documented at surgery. At cardiac catheterization, each of these 7 patients showed elevation and equalization of intracar-

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diastolic pressures within 5 mm Hg, with a characteristic ventricular diastolic "dip and plateau" configuration.

Clinical profiles: Group I consisted of 8 normal volunteers with a mean age of 33 years (range 28 to 47). The mean heart rate was 74 beats/min and the mean respiratory rate was 15 breaths/min. Four volunteers were men and 4 women. Group II included the 14 patients with cardiac tamponade and adequate Doppler studies. The mean age was 49 years (range 30 to 68), the mean heart rate was 113 beats/min and the mean respiratory rate was 25 breaths/min. Five of these 14 patients were male. The etiology of tamponade was malignant in 9 patients, idiopathic in 2, traumatic in 2 and uremic in 1. All group II patients had elevated jugular venous pressure and pulsus paradoxus >10 mm Hg. Four patients had systolic blood pressure <100 mm Hg. Group III consisted of 10 patients with pericardial effusion and no clinical evidence (pulsus paradoxus, systemic hypotension) of tamponade. The mean age was 41 years (range 24 to 69) and 4 were men. The mean heart rate was 78 beats/min and the mean respiratory rate 20 breaths/min. Group IV consisted of 7 patients with surgically documented constrictive pericarditis. The mean age was 55 years (range 13 to 75) and 5 of the patients were men. All 7 patients were in sinus rhythm, the mean heart rate was 88 beats/min and the mean respiratory rate 20/min. The etiology was idiopathic in 5 and malignant in 2. None of these group IV patients had pericardial effusions by echocardiography.

Instrumentation: After a complete clinical echocardiogram, the SVC was imaged from the right supraclavicular window using a Hewlett-Packard 77020A ultrasound instrument with either a 2.5 or 3.5 MHz duplex transducer. Patients lay supine, with head elevated as desired for comfort. The sample volume was placed in the SVC at a depth of 4 to 7 cm to obtain an optimal Doppler flow signal (Figure 1). The Doppler tracings were recorded on a strip chart recorder at 50 mm/s. Doppler filter settings were generally set at the lowest

level (5 or 10 cm/s) to exclude background noise while detecting low venous flow velocities. An electrocardiographic lead displaying a clear T wave was selected and the end of the T wave was used to define end-systole. When necessary, a simultaneous A_2 phonocardiogram was also recorded to define end-systole. As a monitor of respiration, chest wall motion was recorded simultaneously on the Doppler tracings by a Hewlett-Packard pulse transducer taped to the right anterior chest wall. Comparison with simultaneous pulmonary wedge pressure recordings indicated a phase delay in the chest wall recording of <200 ms.

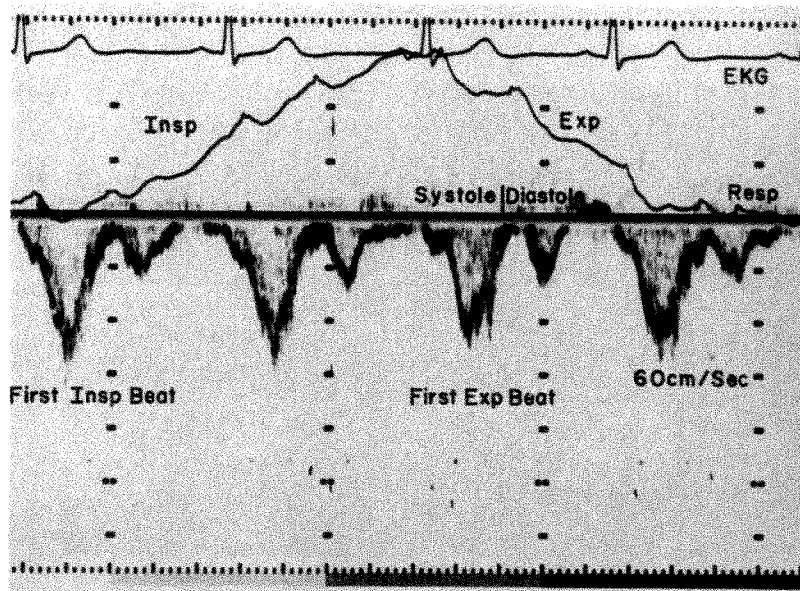
Analysis: Flow velocities varied somewhat throughout the respiratory cycle in normal subjects and to a great extent in some of the patients (Figures 2 and 3). To standardize measurement of these flow velocities, we only measured systolic and diastolic flow velocities from the first inspiratory and expiratory cardiac cycles. A "first" inspiratory or expiratory cardiac cycle was defined as beginning with the first QRS on the inspiratory upstroke or expiratory downstroke of the respiratory tracing (Figure 1).

Velocity measurements in this study included the following: first expiratory diastolic (D_{fe}); first expiratory systolic (S_{fe}); and first inspiratory systolic (S_{fi}). Three parameters were determined for each subject from the following velocity measurements: D_{fe} ; S_{fi}/S_{fe} , which quantitated the respiratory variation in systolic flow; and S_{fe}/D_{fe} , which quantitated the relation between systolic and diastolic velocities in the first expiratory beat. All measurements were performed manually from the strip chart tracings, with mean values determined by averaging velocities from 3 respiratory cycles.

The presence of diastolic right ventricular collapse or right atrial free wall inversion lasting more than one-third of the cardiac cycle was determined by real-time and frame-by-frame analysis of the 2-dimensional echocardiogram.

Statistical significance was first assessed for each parameter from all patients using the Kruskal-Wallis test,

FIGURE 1. Superior vena cava (SVC) Doppler study in a normal adult. Systolic flow velocity exceeds diastolic velocity, with only slight respiratory variation in velocities. Minimum filter setting (5 cm/s) is used to detect low venous flow velocities. During expiration, a small retrograde flow velocity due to atrial contraction is detected (third P wave). EKG = electrocardiogram; Exp = expiration; Insp = inspiration; Resp = respiratory tracing.



a nonparametric equivalent of 1-way analysis of variance to determine overall differences between diagnostic groups. If significant differences were present between groups ($p < 0.01$), individual pairs of groups were compared using the Wilcoxon rank sum test.

RESULTS

Normal subjects: An SVC Doppler study from 1 of the 8 normal subjects (group I) is shown in Figure 1. The electrocardiogram, respirations, first inspiratory beat and first expiratory beat are labeled. From the right supraclavicular window, blood flow down the SVC into the right atrium is away from the transducer and is displayed downward by convention. Flow in all normal subjects was biphasic, with a dominant systolic surge (corresponding to the X-descent of the right atrial pressure waveform) and a lower velocity diastolic surge (corresponding to the Y-descent). Antegrade flow velocities increased slightly during inspiration. Small retrograde SVC flow velocities due to atrial contraction were noted during expiration in some normal subjects, as were small, presystolic antegrade flows due to atrial relaxation (Figure 1). Our findings confirmed those in 40 healthy adults by Appleton et al.⁵

Cardiac tamponade: As in normal subjects, systolic flow was present throughout the respiratory cycle in patients with cardiac tamponade (group II). However, in contrast to normal subjects, diastolic flow could not be detected in the first expiratory beat ($D_{fe} < 5$ to 10 cm/s) during tamponade even when it was preserved during inspiration (Figure 2). The simultaneous right atrial pressure tracing in Figure 2 shows a Y-descent that was similarly preserved during inspiration but markedly blunted in early expiration. When SVC flow reversals

were detected during atrial contraction in patients with tamponade (Figures 2 and 3), they occurred only during early expiration, as reported by Appleton et al.⁴

Diastolic flow in the first expiratory beat was absent in all 14 patients with cardiac tamponade (group II). Results for the first expiratory diastolic velocity (D_{fe}) in all 4 study groups are shown in Figure 4. D_{fe} was significantly decreased in group II only ($p < 0.01$). Actual D_{fe} could not be measured in group II as these velocities were below the selected filter setting in every patient with tamponade. For purposes of analysis, the D_{fe} values in group II were assumed to equal the filter setting used. D_{fe} in group II were thus actually even lower than the estimated value of 9 ± 3 cm/s.

In the only 2 group II patients with acute traumatic tamponade, diastolic velocities were below the filter settings throughout the respiratory cycle. In the 12 group II patients with less acute presentations, only the D_{fe} were below filter settings.

A second feature found in several patients with cardiac tamponade was marked respiratory variation in both systolic and diastolic SVC flow velocities (Figure 3). Because 2 group II patients showed no diastolic flow, we only studied the respiratory variation in systolic flow velocity (S_{fi}/S_{fe}). As shown in Figure 5, respiratory variation was minimal in normal subjects and patients with constrictive pericarditis, significantly increased in patients with pericardial effusion without tamponade ($p < 0.01$) and even greater in patients with cardiac tamponade ($p < 0.01$). However, there was overlap among all 4 groups.

Pericardial effusion without tamponade: In group III, D_{fe} was not significantly different from normal subjects (Figure 4). Respiratory variation in systolic flow

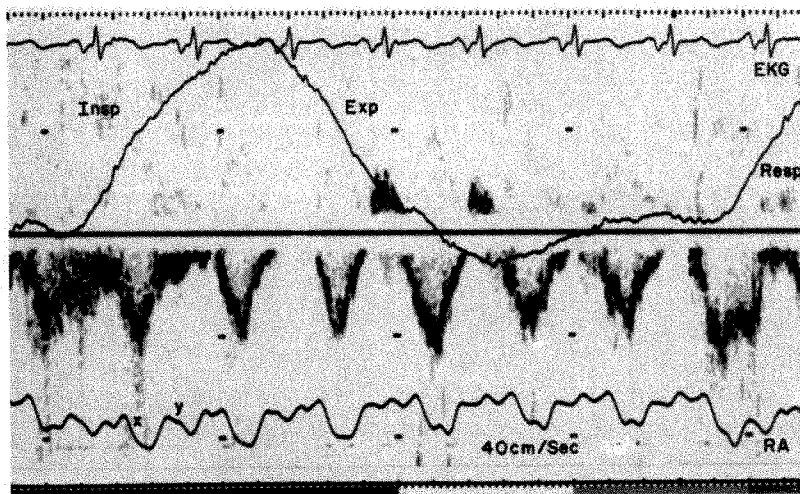


FIGURE 2. Superior vena cava (SVC) Doppler study in patient with cardiac tamponade. The simultaneous right atrial pressure tracing shows preservation of Y-descent during inspiration, but marked blunting of Y-descent during expiration. Absence of diastolic Doppler flow in first expiratory cardiac cycle (D_{fe}) corresponds to blunted Y-descent. Prominent flow reversals due to atrial contraction are seen during early expiration. RA = right atrial pressure tracing; other abbreviations as in Figure 1.

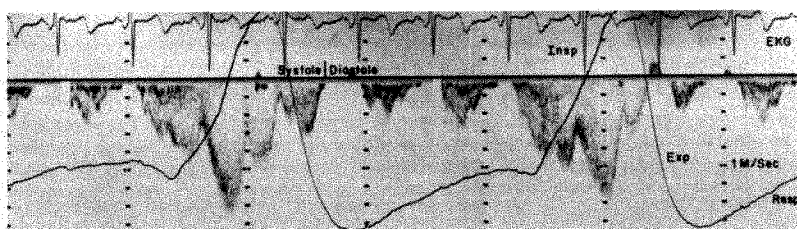


FIGURE 3. SVC Doppler study in patient with cardiac tamponade. There is marked respiratory variation in both systolic and diastolic flow velocities with no antegrade diastolic flow in first expiratory cardiac cycle. Small flow reversals during atrial systole occur in early expiration. Abbreviations as in Figure 1.

velocity was significantly increased in group III, relative to normal subjects ($p < 0.01$), but there was considerable overlap between groups.

Constrictive pericarditis: In 6 of the 7 patients with constrictive pericarditis (group IV), diastolic SVC flow velocity exceeded systolic velocity. Simultaneous right atrial pressure tracings in several patients showed similarly predominant Y-descents throughout the respiratory cycle (Figure 6). In the seventh patient, diastolic velocity approached systolic velocity but did not exceed it ($S_{fe}/D_{fe} = 1.1$). Again, all 7 of these patients were in sinus rhythm.

In contrast to cardiac tamponade, constrictive pericarditis was characterized by prominent diastolic SVC flow velocities in expiration as well as inspiration (Figure 6). The S_{fe}/D_{fe} ratio was ≤ 1.1 in all 7 patients with constrictive pericarditis, as shown in Figure 7. The S_{fe}/D_{fe} ratio in cardiac tamponade was very high, but it was not calculated because D_{fe} decreased below the minimum filter settings. Respiratory variation in systolic velocity was minimal in constrictive pericarditis and S_{fe}/S_{fi} did not differ significantly from normal subjects (Figure 5).

Right atrial and right ventricular collapse: Two-dimensional echocardiograms obtained at the time of the SVC Doppler study in 13 patients with cardiac tamponade and 9 patients with hemodynamically insignificant pericardial effusions were evaluated for right atrial and right ventricular collapse. The right ventricular free wall was adequately visualized in all the echocardiograms. Right ventricular collapse had a specificity of 100% (9 of 9) and a sensitivity of 38% (5 of 13) for the presence of cardiac tamponade. Adequate visualization of the right atrial free wall was more difficult, with technically inadequate studies in 23% (3 of 13) of the patients with cardiac tamponade and in 11% (1 of 9) of

the patients with hemodynamically insignificant pericardial effusions (18% overall). The sensitivity of right atrial collapse for cardiac tamponade was 60% (6 of 10) and the specificity was 50% (4 of 8).

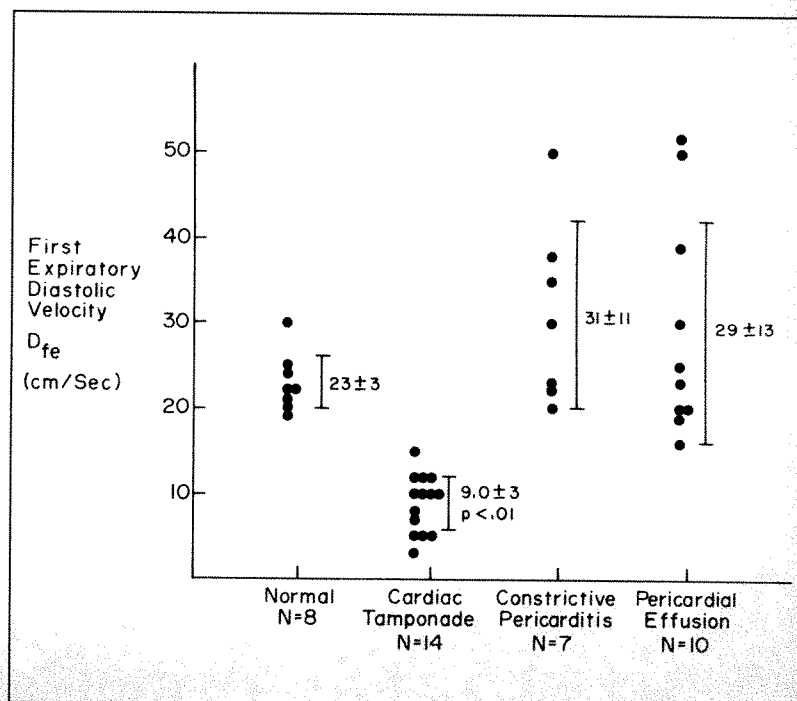
Doppler studies after pericardiocentesis and pericardiectomy: SVC Doppler studies were performed immediately after pericardiocentesis in 5 patients with cardiac tamponade. In 3 of these 5 group II patients, the SVC Doppler pattern normalized, with D_{fe} increasing into the normal range. Intracardiac and intrapericardial pressures decreased to normal in each of these patients. In the other 2 patients, D_{fe} also increased after pericardiocentesis, but to such an extent that diastolic flow velocities became dominant, with S_{fe}/D_{fe} values below 1.0. Despite a decrease in intrapericardial pressure to approximately zero, both patients showed persistent elevation and equalization of intracardiac diastolic pressures consistent with effusive-constrictive pericarditis.

SVC Doppler studies were performed after complete pericardiectomy in 2 patients with constrictive pericarditis. In 1 patient, the SVC Doppler pattern normalized, but in the other patient, the diastolic flow velocity remained predominant after pericardiectomy. Repeat cardiac catheterization in this patient showed persistent elevation and equalization of intracardiac diastolic pressures, with a deep Y-descent in the right atrial pressure tracing. Right ventricular biopsy showed eosinophilic infiltration of the myocardium with interstitial fibrosis, consistent with a restrictive cardiomyopathy. No specific etiology for this patient's combined pericardial and myocardial disease was found.

DISCUSSION

In this study, Doppler ultrasound of the SVC allowed noninvasive, quantitative analysis of flow abnormalities that distinguished patients with cardiac tam-

FIGURE 4. First expiratory diastolic velocities (D_{fe}) were significantly lower in patients with cardiac tamponade than in other patient groups. Values are mean velocity $\pm$ standard deviation.



ponade and constrictive pericarditis from normal subjects and patients with hemodynamically insignificant pericardial effusions.

Superior vena cava Doppler in cardiac tamponade and pericardial effusion: Studies of acute cardiac tamponade in dogs have shown that as intrapericardial pressure increases, the right atrial Y-descent is progressively obliterated.⁶ During systole, right ventricular ejection decreases intracardiac volume and thus lowers intrapericardial and right atrial pressure, preserving systolic right atrial filling (the X-descent). Because intracardiac volume does not change during diastole, intrapericardial and right atrial pressures do not decrease and the Y-descent is blunted. A corresponding decrease in diastolic SVC flow has been shown by invasive methods² and was shown in several of our patients by simultaneous SVC Doppler and right atrial pressure recordings (Figure 2).

Only the 2 patients with acute traumatic tamponade showed absent SVC diastolic forward flow velocities throughout the respiratory cycle. The other 12 patients with cardiac tamponade showed some inspiratory augmentation of diastolic SVC flow into the right atrium but severely decreased diastolic first expiratory flow velocities ($D_{fe} = <9 \pm 3$ cm/s, $p < 0.01$). D_{fe} in patients with hemodynamically insignificant pericardial effusions were not significantly different from normal (29 ± 13 vs 23 ± 3 cm/s).

Relation to previous studies of cardiac tamponade: This study confirms previous suggestions that right ventricular diastolic collapse is a much less sensitive sign of cardiac tamponade in hospitalized patients than in canine studies of acute tamponade.⁷ Echocardiographic right ventricular collapse had a specificity of 100% and a sensitivity of 38% in our patients. Prolonged inversion of the right atrium⁸ proved neither sensitive (60%) nor specific (50%) in this study, and it could not be ade-

quately assessed in 23% of the patients with tamponade. These findings support another recent study of echocardiographic indicators of tamponade⁹ and suggest the importance of Doppler assessment of venous return in these patients.

Increased respiratory variation in Doppler transtricuspid and transpulmonic valve flows has been reported in patients with cardiac tamponade.^{5,10} Transvalvular flows were not evaluated here, but a spectrum of changes in the respiratory variation of SVC flow velocities was shown (Figure 5). There was little respiratory variation among normal subjects and patients with constrictive pericarditis, but respiratory variation increased in patients with hemodynamically insignificant pericardial effusions and was greatest in cardiac tamponade. Marked respiratory variation in vena cava, transtricuspid and transpulmonic valve flow velocities has been reported in studies of patients with cardiac tamponade, reflecting augmentation of compromised right-sided heart filling by the normal inspiratory fall in intrapleural pressure.^{5,10,11} In these same studies, respiratory variation in flow velocities among patients with hemodynamically insignificant pericardial effusions was inconsistent. Increased respiratory variation among these patients in our study may indicate very early hemodynamic compromise or simply reflect increased respiratory depth in some patients.

The only element of increased respiratory variation in SVC flow that contributed significantly to the diagnosis of cardiac tamponade in this study was loss of diastolic flow in the first expiratory beat (D_{fe} , Figure 4). This supports similar observations by Appleton et al⁴ in patients with cardiac tamponade, although D_{fe} were not quantitated in that study and large inspiratory increases in SVC flow were not noted. In this study, all D_{fe} in patients with cardiac tamponade were below 15 cm/s (mean 9 ± 3), while D_{fe} in patients with hemodynami-

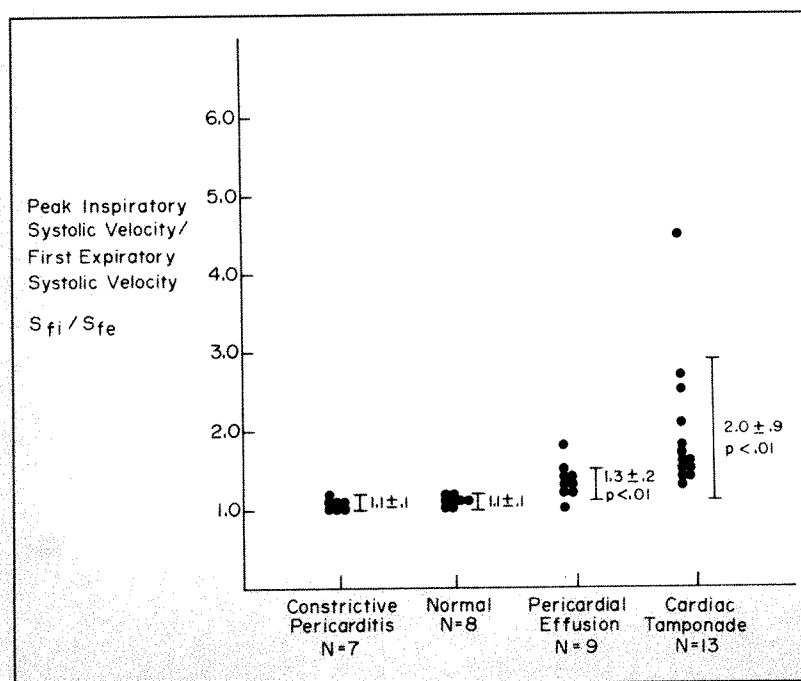


FIGURE 5. Ratio of first inspiratory to first expiratory systolic velocities (S_{fi}/S_{fe}) shows that there is little respiratory variation in flow velocities among normal subjects and patients with constrictive pericarditis. This ratio is significantly elevated in patients with pericardial effusions and even higher in patients with cardiac tamponade. However, there is overlap between groups. Values are mean $\pm$ standard deviation.

cally insignificant pericardial effusions were above that threshold (mean 29 ± 13 cm/s). These D_{fe} in the SVC are similar to hepatic vein velocities reported in 9 patients with tamponade (6 ± 8 cm/s).¹¹ Hepatic vein Doppler measurements are technically adequate in up to 50% of patients with pericardial effusion, providing an alternative approach when SVC flow is unobtainable.^{4,5,11}

Severely abnormal relaxation due to right ventricular hypertrophy may abolish diastolic right atrial filling and mimic cardiac tamponade.¹² Patients with chronic obstructive lung disease may show low D_{fe} as well, but generally their diastolic flow velocities are most severely reduced 2 or 3 beats after expiration begins.¹¹ In these situations, reciprocal variation in mitral and tricuspid valve flow velocities with respiration may prove a more reliable indicator of tamponade.^{4,11} Importantly, our method of respiratory monitoring with the pulse transducer available on many echocardiographic instruments may provide a simple alternative to the separate nasal thermistor-based device used in earlier studies.^{4,5,11}

Superior vena cava Doppler in constrictive pericarditis: Invasive studies in constrictive pericarditis have shown that the rapid early diastolic decrease in right atrial pressure (Y-descent) simultaneously augments the diastolic SVC flow velocity.¹ In this study, predominant diastolic SVC velocities were seen only in patients with constrictive pericarditis (Figures 6 and 7). As all these patients were in sinus rhythm, predominant diastolic SVC flow velocities were not related to loss of atrial relaxation, as in atrial fibrillation¹ or after open-heart surgery.¹³ They were also unrelated to moderate to severe tricuspid regurgitation, which was excluded by Doppler examination, or right ventricular infarction.¹²

One patient in this study showed persistent restrictive physiology after surgical relief of constrictive pericarditis, and myocardial biopsy confirmed an eosinophilic restrictive cardiomyopathy. Like the right atrial pressure tracings, SVC Doppler studies performed before and after pericardiectomy in this patient could not be distinguished. In both instances, diastolic SVC flow was predominant during both expiration and inspiration (Figure 6), as previously noted by Shabetai et al² and others.^{1,13} Transvalvular Doppler studies may distin-

guish constrictive pericarditis from restrictive cardiomyopathy by showing reciprocal respiratory changes in mitral and tricuspid flow due to enhanced diastolic interaction within the confining pericardium.¹⁴ Importantly, whenever mean right atrial pressure is elevated, the X-descent may be blunted due to either diminished atrial contraction and relaxation or poor systolic descent of the base.¹³ Predominant diastolic SVC flow velocities will thus lack specificity in such patients, but they will indicate the need for further evaluation, such as a transvalvular Doppler study with respiratory monitoring.¹⁴

Finally, not all patients with constrictive pericarditis have a dominant right atrial Y-descent at catheterization.¹⁵ Pericardial effusions may blunt the Y-descent in effusive-constrictive pericarditis.^{16,17} In those few pa-

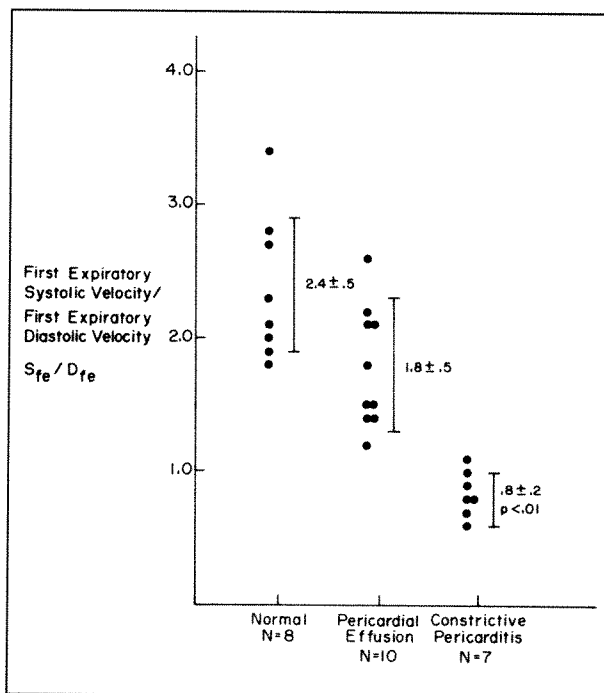
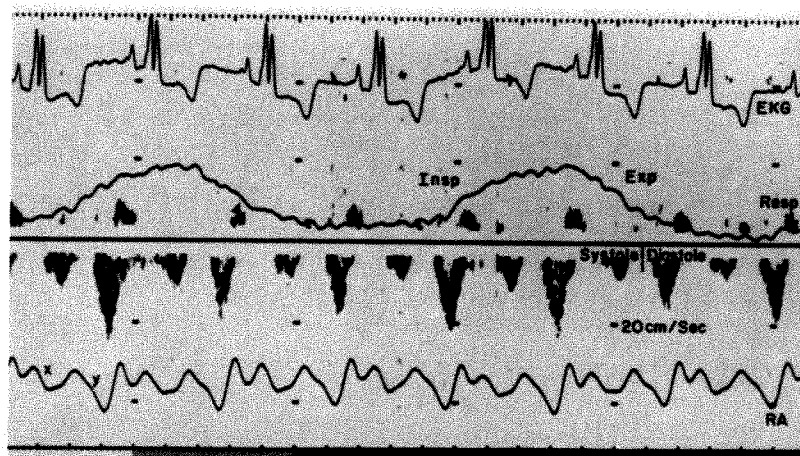


FIGURE 7. Ratio of systolic to diastolic first expiratory flow velocities (S_{fe}/D_{fe}) was significantly lower in patients with constrictive pericarditis than in normal subjects or patients with hemodynamically insignificant pericardial effusions. Values are mean $\pm$ standard deviation.

FIGURE 6. Superior vena cava (SVC) Doppler study in patient with constrictive pericarditis. Simultaneous right atrial pressure and Doppler tracings show a dominant Y-descent and predominant diastolic SVC flow velocity throughout respiratory cycle. Abbreviations as in Figure 2.



tients with "occult" constrictive pericarditis, a prominent Y-descent may appear only after volume loading.¹⁸ Because the Y-descent correlates closely with the diastolic SVC flow velocity (Figure 6), some patients with constrictive pericarditis may show higher S_{fe}/D_{fe} than were seen in our patients with constrictive pericarditis. None of these 7 patients had pericardial effusions or required volume loading to show their constrictive physiology.

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Transient Alterations in Cardiac Performance After a Six-Hour Race

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Ten long distance runners were enrolled in a 6-hour competitive race. Immediately after the race technetium-99m-albumin gated blood pool scans were performed and indium-111 antimyosin was injected. Forty-eight hours later antimyosin scans were obtained and control gated blood pool scans were performed. Left ventricular ejection fraction was higher after the race (65 ± 5 vs $60 \pm 7\%$, $p < 0.01$) due to a decrease in end-systolic counts. Right ventricular ejection fraction was lower after the race (42 ± 7 vs $54 \pm 12\%$, $p = 0.03$) due to an increase in both end-diastolic and end-systolic counts. A longer systolic period was observed after the race ($53 \pm 5\%$ of the RR interval vs $39 \pm 3\%$, $p = 0.005$). No significant differences were observed in peak filling or peak emptying rates after the race. An increase in pulmonary blood volume (116% of control) was observed after the race. Antimyosin scans were normal in 7 athletes and minimal antimyosin myocardial uptake was seen in 3. Transient alterations in biventricular performance present after the race correspond to functional adaptation to strenuous exercise and are not due to irreversible myocyte damage.

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Ultramarathon running (covering distances >26.5 miles) is known to produce impaired resting left ventricular performance.¹ A reduction of end-diastolic dimension with slight increase in end-systolic dimension has been observed after a 24-hour run.¹ A decrease in left ventricular fractional shortening and in mean velocity of circumferential fiber shortening has been observed after prolonged strenuous running on a treadmill.² It is not known if myocyte injury can be induced by exhaustive long distance running. Indium-111 antimyosin is specific for myocyte necrosis, and has emerged as a sensitive agent to detect infarct,³ myocarditis⁴⁻⁵ and cardiac transplant rejection.⁶ The purpose of this study was to investigate biventricular performance after a 6-hour race by equilibrium gated blood pool scans, to assess reversibility of abnormalities 48 hours later and to look for the presence of irreversible myocardial injury immediately after the race by means of indium-111 antimyosin scintigraphy.

METHODS

Ten healthy amateur ultramarathon male runners, 26 to 46 years old, were enrolled in an official 6-hour competitive race around our hospital perimeter. The race took place from 11 A.M. until 5 P.M. on February 25, 1989. The temperature was 13 to 15°C with a mean humidity of 84%. The circuit was 1,454 meters long with 720 meters at a grade of 6.8%. A rain shower lasted 20 minutes during the race.

Procedure: Immediately after finishing the race each athlete was given 25 mCi of technetium-99m albumin intravenously. With the athletes supine, gated blood pool scans were acquired with a large field-of-view camera (Siemens Orbiter ZLC linked to a Siemens Microdelta computer) in the 30 to 50° left anterior oblique projection with 5 to 10° of caudal tilt. The cardiac cycle was separated into 30 64×64 frames, with at least 300,000 counts collected in each frame. When gated blood pool scans were finished, 2 mCi of indium-111 antimyosin (0.5 mg of R11D10-Fab DTPA, supplied by Centocor in individual doses) was injected. Blood samples were simultaneously withdrawn to determine creatine kinase levels and MB fractions.

Athletes returned 48 hours later to undergo antimyosin scans. Planar anterior views of the thorax were acquired using the same instrumentation. When antimyosin scans were finished, gated blood pool scans were again performed to be used as control scans to assess reversibility of abnormalities.

Interpretation of gated blood pool scans: Left ventricular ejection fraction was measured using a semiau-

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tomatic edge detection and counts technique with a varying region of interest. Fourier analysis was also used to derive peak filling and peak emptying rates as well as time-to-peak from the time-activity curve.⁷ Right ventricular ejection fraction was determined using a double region of interest technique after background subtraction.⁸ End-diastolic and end-systolic frames in the postrace and control studies were respectively count-normalized to compare end-diastolic and end-systolic background-corrected counts in the ventricular region, as well as stroke counts between both studies. Time to reach end-systole is expressed as percentage of the RR time interval. Blood volume in the lungs was assessed in the normalized end-diastolic frames using the method of Okada et al,⁹ tracing a region of interest over the left lung adjacent to the aorta. An index was obtained by dividing counts in the postrace study by counts in the control study.

Interpretation of antimyosin studies: The presence of antimyosin uptake in the heart was assessed comparing average counts/pixel in the heart with average counts/pixel in the lungs. Heart-to-lung ratio 48 hours after injection in normal subjects is 1.46 ± 0.4 .¹⁰

Statistical analysis: Nonparametric analysis of groups using the Mann-Whitney and Wilcoxon tests was performed. Regression analysis was used to assess correlation between variables.

RESULTS

The athletes covered a mean distance of 54.7 kilometers (range 46.5 to 69.8) during the race. Heart rate after the race when gated blood pool scans were first acquired was 88 ± 8 beats/min, and 56 ± 7 beats/min during the control study 48 hours later ($p < 0.01$). Blood pressure was lower after the race (mean 110/65 mm Hg after the race and 127/80 mm Hg 48 hours later). The mean weight loss of the athletes after the race was 1,200 g (range 280 to 3,000).

Left ventricular ejection fraction was $65 \pm 5\%$ after the race, and $60 \pm 7\%$ ($p < 0.01$) in the control study (Table I). This was because of a decrease in end-systolic counts without significant change in end-diastolic counts (Figure 1). End-diastolic counts after the race were $8,300 \pm 1,260$, and $8,500 \pm 1,300$ in the control study. End-systolic counts after the race were $2,850 \pm 512$, and $3,440 \pm 660$ in the control study ($p < 0.01$).

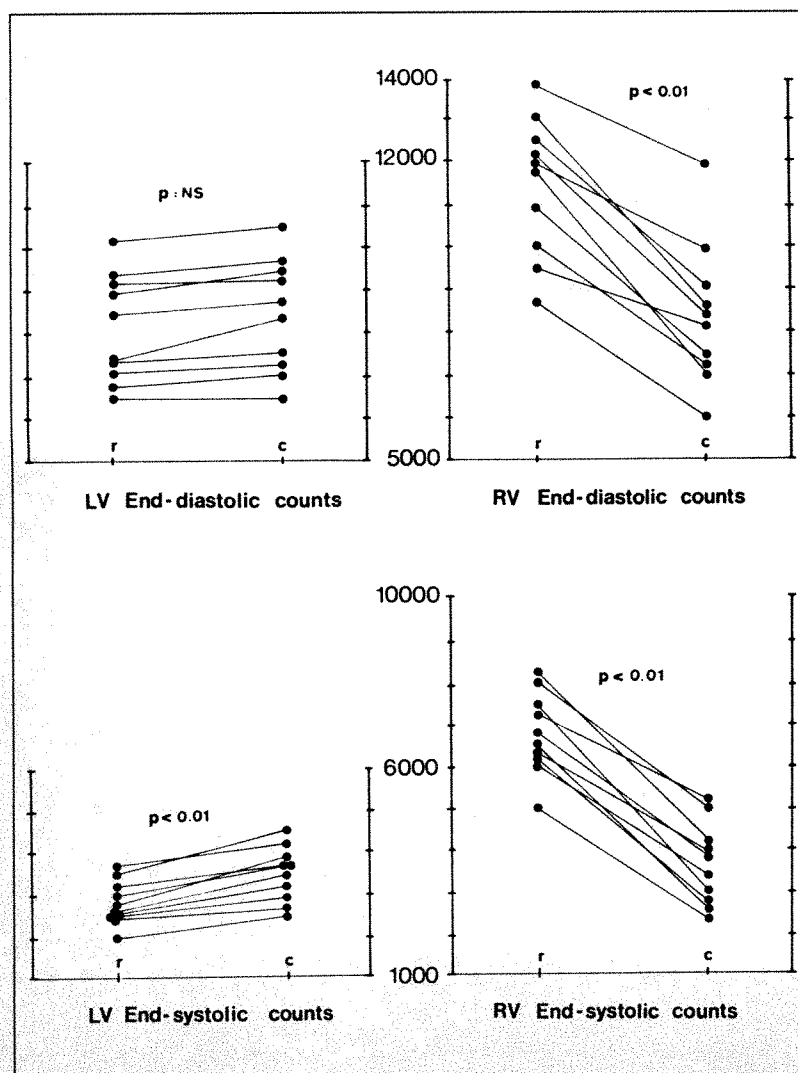


FIGURE 1. Left ventricular (LV) and right ventricular (RV) end-diastolic and end-systolic counts after the race (r) and in the control study (c). NS = not significant.

TABLE I Cardiac Parameters Determined After the Race (r) and in the Control Study (c) 48 Hours Later

No.	Km	HR		LVEF		RVEF		% Systole		CK	(%MB)	HLR	PBVR
		r	c	r	c	r	c	r	c				
1	53.8	97	47	63	57	41	39	56	39	1,745	2.5	1.4	1.16
2	59.6	94	64	61	55	46	62	58	37	171	6.4	1.25	1.36
3	63.9	77	48	58	52	33	59	50	38	380	5.3	1.7	1.36
4	47.9	99	47	71	61	37	62	58	35	165	5.5	1.54	1.16
5	50.8	80	52	71	70	46	66	56	39	409	2.4	1.5	1.05
6	69.8	82	58	70	72	58	64	52	37	603	2.8	1.48	1
7	59.6	93	59	67	60	32	32	50	37	—	—	1.75	1.23
8	49.4	92	64	68	59	42	49	56	42	294	6.5	1.52	1.38
9	46.5	78	54	59	64	43	45	44	41	425	2.1	1.7	0.9
10	45.1	83	64	64	54	45	64	50	44	285	3.2	1.25	1
Mean	54	87	55	65	60	42	54	53	39	498	4	1.51	1.16
SD	8	8	7	4	6	7	12	5	3	—	—	0.18	0.17

HLR = heart-to-lung ratio in the antimyosin scan; HR = heart rate (beats/min); Km = kilometers covered during the race; LVEF = left ventricular ejection fraction in %; PBVR = pulmonary blood volume ratio; RVEF = right ventricular ejection fraction in %; SD = standard deviation.

Right ventricular ejection fraction was $42 \pm 8\%$ after the race, and $54 \pm 12\%$ ($p = 0.03$) in the control study (Table I). This was because of an increase of end-diastolic and end-systolic counts after the race, without significant change in stroke counts (Figure 1). End-diastolic counts after the race were $11,800 \pm 1,710$, and $8,490 \pm 1,700$ in the control study ($p < 0.01$). End-systolic counts after the race were $6,840 \pm 980$, and $3,930 \pm 970$ in the control study ($p < 0.01$).

Blood volume in the lungs was higher after the race (index 1.16 ± 0.17) (Table I). Individual indexes did not correlate with decrease in right ventricular ejection fraction after the race.

Peak emptying rate (expressed as end-diastolic volumes/s) after the race was 4.5 ± 0.8 and 4.3 ± 0.9 in the control study (difference not significant). Peak filling rate after the race was 3.7 ± 0.8 and 3.5 ± 0.6 in the control study (difference not significant). Time to peak and time to end-systole were shorter after the race but in relation to the faster heart rate. The percentage of systolic time was significantly larger after the race (53 ± 5 vs $39 \pm 3\%$; $p = 0.005$) (Figure 2).

Absolute creatine kinase values and MB fraction were elevated after the race (mean creatine kinase 498 U/liter, range 165 to 1,745; mean MB 10.5 U/liter, range 9 to 43), with a mean percentage of MB of 4.07%.

Heart-to-lung ratio in antimyosin scans was 1.51 ± 0.18 (difference not significant vs control subjects¹⁰) (Table I). Taking a ratio > 1.58 as a cutoff point (mean ratio in normal subjects + 3 standard deviations),⁵ antimyosin scans were normal in 7 athletes and showed minimal myocardial uptake in 3 (heart-to-lung ratios from 1.7 to 1.75).

DISCUSSION

Increase in pulmonary blood volume with supine exercise has been found in patients with coronary disease and is thought to be in relation to deterioration of left ventricular function, volume or pressure-overload or decrease in left ventricular compliance.^{9,11} More recently, the increase in pulmonary blood volume after upright exercise in normal subjects has been described,¹² and

explained as due to capillary recruitment and increased lung perfusion associated with high-level exercise. In the study of Froelich et al¹² the increase in pulmonary blood volume was higher than ours (128% of control),

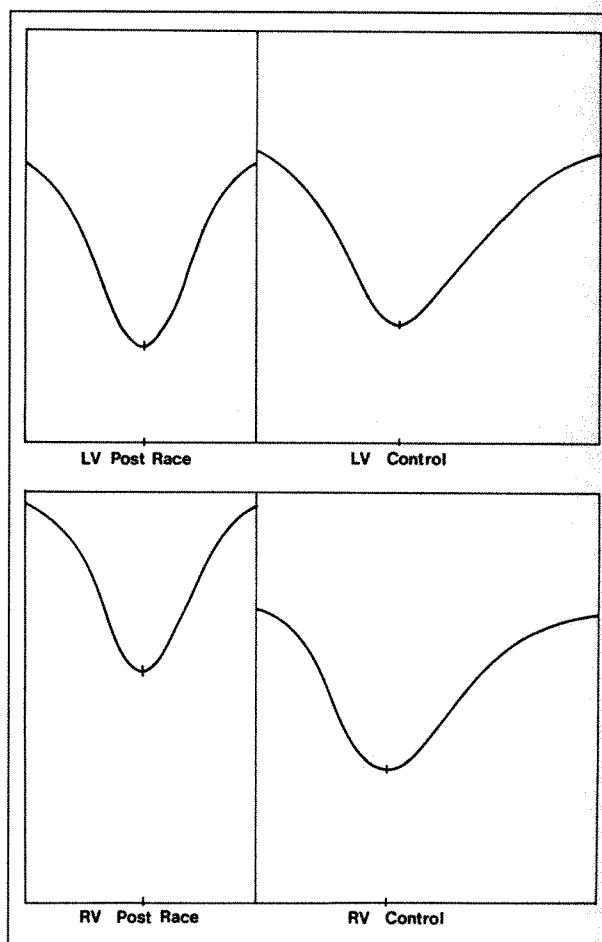


FIGURE 2. Cardiac cycle reconstructed from measured ventricular counts after the race (average RR interval of 685 ms) and in the control study (average RR interval of 993 ms). LV = left ventricle; RV = right ventricle. Percentage of systolic time after the race was $53 \pm 5\%$, and it was $33 \pm 3\%$ in the control study ($p = 0.005$).

but it was measured at point of exhaustion during progressive pedaling. Our data support the concept that increased pulmonary blood volume with prolonged exercise can be a normal response and does not indicate left ventricular failure per se.

The relative lengthening of the systolic period is consistent with the increase in the ratio of contraction time to relaxation time as heart rate increases.¹³ An increase of the systolic period from 39 to 53% could seem excessive given an increase of heart rate from 56 to 88 beats/min. However, the increase in relative systolic time observed after the race can also be in relation to the decrease in peripheral resistances after long distance running, and subsequent lengthening of the passive phase of the systolic period. Prior studies have interpreted the decrease in stroke dimension with increase¹ or no change² in end-systolic dimension observed after prolonged exercise as due, at least in part, to a depressed inotropic state. Free fatty acid elevation after prolonged running could cause a depression of the inotropic state.¹⁴ We have observed slight increase in stroke counts with decrease in end-systolic counts resulting in an increased left ventricular ejection fraction immediately after the race, probably because of less prolonged¹ and non-exhaustive² exercise.

The decrease in right ventricular ejection fraction immediately after the race was a result of an increase in both end-diastolic and end-systolic counts without change in stroke counts. This suggests transient dilatation of the right ventricle after the race. This can be due to a depression in the contractile state resulting in an increase in end-diastolic volume to maintain stroke volume, or to adaptation to changes in preload and afterload. Preload of the right ventricle during the race is increased due to the increase in venous return. But right ventricular function is more dependent on afterload.¹⁵ With increased right ventricular afterload, right ventricular ejection fraction decreases.¹⁶ The presence of increased pulmonary volume could suggest increase in afterload of the right ventricle during the race, despite the lack of correlation with individual decrease in right ventricular ejection fraction.

The increase in total creatine kinase after the race indicates skeletal muscle injury. A similar increase in MB fraction has been described and is thought to be noncardiac in origin.¹ Normal antimyosin studies in 7 athletes after the race indicate that no myocyte damage had occurred in these subjects. The 3 mildly positive antimyosin studies raise the question of the presence of subtle myocardial damage. We have shown that antimyosin studies can detect variable degrees of myocyte damage in different cardiomyopathies.^{6,7,11} One athlete

(no. 9) reported a history of important alcohol intake (>80 g/day). Alcohol can produce myocardial damage¹⁷ and this could account for the positive antimyosin study. The other 2 athletes had no special characteristics. The significance of these mildly positive antimyosin studies remains to be elucidated since until now no cardiomyopathies have been associated with long distance running.

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The Electrocardiogram at Rest and Exercise During a Simulated Ascent of Mt. Everest (Operation Everest II)

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To evaluate the effect of extreme altitude on cardiac function in normal young men, electrocardiograms were recorded at rest and during maximal exercise at several simulated altitudes up to the equivalent of the summit of Mt. Everest (240 torr or 8,848 m). The subjects spent 40 days in a hypobaric chamber as the pressure was gradually reduced to simulate an ascent. Changes in the resting electrocardiogram were evident at 483 torr (3,660 m) and were more marked at 282 torr (7,620 m) and 240 torr (8,848 m). They consisted of an increase in resting heart rate from 63 ± 5 to a maximum of 89 ± 8 beats/min; increase in P-wave amplitude in inferior leads; right-axis shift in the frontal plane; increased S/R ratio in the left precordial leads; and increased T negativity in V_1 and V_2 . No significant arrhythmias or conduction defects were observed. Most changes reverted to normal within 12 hours of return to sea level, with the exception of the frontal-plane axis and T-wave alterations. Maximal cycle ergometer exercise at 282 torr (7,620 m) and 240 torr (8,848 m) resulted in a heart rate of 138 ± 7 and 119 ± 6 beats/min at the 2 altitudes, respectively. No ST depression or T-wave changes suggestive of ischemia occurred despite a mean arterial oxygen saturation of 49% and a mean pH of 8 during peak exercise. Occasional ventricular premature beats were observed during exercise in 2 subjects. It is concluded that extreme altitude exposure results in electrocardiographic changes compatible with pulmonary hypertension and that maximal exercise at 8,848 m is not accompanied by any electrocardiographic evidence of ischemia despite severe hypoxemia and alkalosis.

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Several electrocardiographic studies have been performed at high altitudes during expeditionary climbs. Observed changes include an increase in heart rate, a right-axis frontal plane QRS shift, increased P-wave amplitude in inferior leads, increased S-wave amplitude in left precordial leads, T-wave inversion in right precordial leads and, occasionally, right ventricular conduction delays.¹⁻⁷ A recent hypobaric chamber study, "Operation Everest II," provided an opportunity to study human physiologic responses to simulated altitudes up to 8,848 m (29,028 feet). During the study healthy men were exposed to a gradual reduction in atmospheric pressure over a 40-day period using an ascent profile similar to several Everest climbs. Resting electrocardiograms were recorded at 4 altitudes. Additional electrocardiograms were recorded during maximal exercise at 2 altitudes. The results permit a more complete evaluation of cardiac function at very high altitudes than was previously possible.

METHODS

Eight healthy men aged 21 to 31 years began the study after giving informed consent. None had any history of cardiopulmonary disease or contraindications to altitude exposure. All had normal physical examinations, chest roentgenograms, resting electrocardiograms and normal values on standard laboratory screening tests before the study. All were physically fit, and most had previously competed in endurance sports. None had been exposed to altitudes of $>3,000$ m in the previous 6 months, although 2 had previous mountain climbing experience above 6,000 m.

After several days of sea level studies, the subjects entered a large hypobaric chamber at the United States Army Research Institute of Environmental Medicine in Natick, Massachusetts, where they remained for 40 days while the chamber was gradually decompressed to a pressure of 240 torr, which is equivalent to the summit of Mt. Everest.

The measured barometric pressure on the summit of Mt. Everest is 253 torr (PIO_2 43 torr). However, at the highest altitudes in Operation Everest II only a small study chamber was used and its ventilation system was inadequate to eliminate all the oxygen exhaled by the scientists wearing oxygen masks. As a result the inspired oxygen rose to 22%. By lowering the chamber pressure to 240 torr, the inspired oxygen pressure was maintained at 43 torr.

While in the chamber the subjects had ad libitum access to a nutritionally balanced diet and were able to exercise daily on a cycle ergometer, a treadmill or a climbing ergometer (Versaclimber) when not involved in testing. Two subjects were removed from the study, 1 at 380 torr and the other at 282 torr, after transient acute hypoxic episodes. One subject experienced a brief loss of consciousness and disorientation and another had a brief period of confusion. Both responded promptly to supplemental oxygen, recompression and removal from the chamber. A more detailed account of the test subjects and conditions of exposure has been published.⁸

Standard 12-lead electrocardiograms with the subject in a supine position were obtained at sea level (50 m) before ascent, at 483 torr (3,660 m), 412 torr (4,900 m), 347 torr (6,100 m), 282 torr (7,620 m), 240 torr

(8,848 m) and again at sea level 12 hours after descent using a Quinton model 630 A electrocardiographic recorder. All 8 subjects had sea level recordings. Seven subjects had recordings at all altitudes. One subject had recordings at 3,660 m, 4,900 m and 6,100 m and 1 only had recordings at 4,900 m and 6,100 m. Twelve-lead electrocardiograms were obtained in 6 subjects and limb lead tracings in 1 subject at rest and during exercise on an upright cycle ergometer at 289 torr (7,450 m). Three of these 6 had repeat studies (2 with 12 leads and 1 with limb leads) performed at 8,848 m.

All electrocardiograms were read independently by 3 physicians who were unaware of the altitude at which the tracings were recorded. The QT interval was corrected for heart rate. Measurements made on the resting electrocardiograms included heart rate over 10 consecutive cycles, P-wave amplitude (mV) in leads II, III and aVF, P-wave amplitude (mV) and direction in V₁ and V₂, S/R ratio in V₆, T-wave direction and amplitude (mV) in V₁ and V₂, frontal plane axis, PR interval and QTc interval.

Exercise electrocardiograms were examined for arrhythmias and changes in T wave or ST segment. The maximal heart rate and QT interval were measured and the axis in the frontal plane was determined.

Pulmonary artery pressure and pulmonary artery wedge pressures were recorded by a Swan-Ganz flow-directed catheter inserted into a forearm vein and advanced to the pulmonary artery. Exercise was performed using a cycle ergometer (Monark "Pedal-mate"). The maximal exercise workload lasted 3 to 8 minutes. Further details of the methods have been published.⁸

Data are expressed as mean $\pm$ standard error of the mean except where noted. Data were analyzed using a 1-way analysis of variance.

RESULTS

Resting electrocardiograms: The results of the analysis of resting electrocardiograms are summarized in Table I and Figures 1 through 7. Resting heart rates increased from 63 ± 5 beats/min at sea level to a maximum of 89 ± 8 beats/min at 7,620 m ($p < 0.005$). Upon return to sea level the mean heart rate decreased to 61 ± 8 beats/min. There were no significant increases in heart rate up to 4,900 m but at 6,100 m and 7,620 m the rate increased sharply (Figure 1). The P-wave amplitude in leads II, III and aVF increased significantly ($p < 0.005$) at 3,660 m and continued to increase up to 8,848 m. There was a decrease in preascent amplitudes upon return to sea level (Figure 2). The changes in amplitude were similar in all 3 inferior leads (Table I).

P waves were initially upright in leads V₁ and V₂ but became progressively lower and finally negative at 6,100 m. Upon return to sea level the P waves were again upright, but with a lower amplitude than before ascent (Figure 3).

S waves appeared in left precordial leads with ascent. As measured by the S/R ratio in V₆, S waves became most prominent at 6,100 m with little change

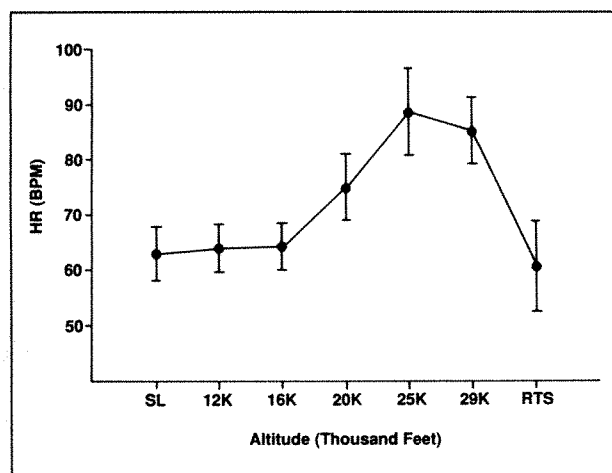


FIGURE 1. Resting heart rates at sea level and 5 altitudes. Barometric pressures (torr) for each altitude are: SL = 760, 12 k = 483, 16 k = 412, 20 k = 347, 25 k = 282, 29 k = 240. Brackets indicate 1 standard deviation. RTS = 24 hours after return to sea level; SL = sea level.

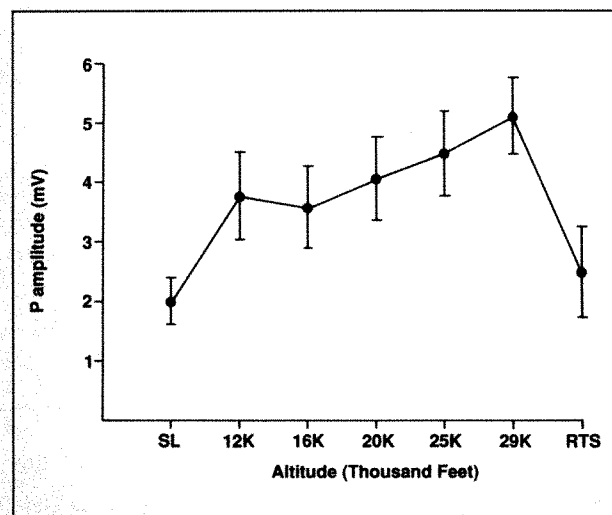


FIGURE 2. Sum of the amplitude of P waves in leads II, III and aVF at sea level and 5 altitudes. Abbreviations and symbols as in Figure 1.

TABLE I Resting Electrocardiographic Values at Sea Level and Five Altitudes

		760 torr	483 torr	412 torr	347 torr	282 torr	240 torr	
		SL	12,000 ft	16,000 ft	20,000 ft	25,000 ft	29,000 ft	RSL
		(n = 8)	(n = 8)	(n = 8)	(n = 7)	(n = 6)	(n = 6)	(n = 6)
P wave	II (mV)	1.09 ± 0.11	1.47 ± 0.27	1.44 ± 0.34	1.81 ± 0.29	1.80 ± 0.25	2.05 ± 0.27	1.03 ± 0.25
	III (mV)	0.29 ± 0.30	0.91 ± 0.28	0.76 ± 0.19	1.04 ± 0.20	1.30 ± 0.20	1.50 ± 0.22	0.63 ± 0.24
	aVF (mV)	0.75 ± 0.12	1.00 ± 0.28	1.18 ± 0.25	1.24 ± 0.21	1.08 ± 0.33	1.58 ± 0.20	0.83 ± 0.28
II + III + aVF (mV)		2.0 ± 0.39	3.77 ± 0.74	3.58 ± 0.69	4.07 ± 0.71	4.5 ± 0.72	5.13 ± 0.65	2.5 ± 0.76
	V ₁ (mV)	0.44 ± 0.18	0.38 ± 0.18	0.13 ± 0.1	-0.36 ± 0.14	-0.17 ± 0.17	-0.12 ± 0.08	0.17 ± 0.11
	V ₂ (mV)	0.79 ± 0.13	0.79 ± 0.16	0.36 ± 0.11	0.26 ± 0.09	0.43 ± 0.04	0.22 ± 0.15	0.65 ± 0.17
S/R in V ₆ (%)		14.9 ± 2.4	17.5 ± 2.1	18.4 ± 2.9	30.7 ± 6.4	28.8 ± 7.7	28.9 ± 0.8	12.6 ± 6.5
	(beats/min)	62.9 ± 4.8	63.9 ± 4.3	64.3 ± 4.2	75.0 ± 6.0	88.8 ± 7.9	85.3 ± 6.0	60.8 ± 8.1
T wave	V ₁ (mV)	0.44 ± 0.69	0.79 ± 0.15	0.38 ± 0.35	-0.36 ± 0.38	-1.0 ± 0.26	-0.58 ± 0.63	-2.42 ± 0.38
	V ₂ (mV)	5.44 ± 0.85	5.69 ± 0.79	3.94 ± 1.39	2.64 ± 0.58	3.33 ± 0.62	3.25 ± 0.44	1.42 ± 0.62
	Axis (°)	54.4 ± 9.9	62.8 ± 6.16	67.75 ± 4.9	77.6 ± 9.8	98 ± 5.9	107 ± 7.83	89.9 ± 9.43

Data are mean ± standard error of the mean. HR = heart rate; P = P wave; S/R = ratio of S-wave to R-wave amplitude; T = T wave.

thereafter. The S/R ratio returned to the preascent value upon return to sea level (Figure 4).

T waves in lead V₁ were initially upright but became negative at 6,100 m. They remained negative throughout the rest of the ascent and were more deeply negative after return to sea level (Figure 5). T waves in lead V₂ showed a decrease in amplitude but did not become negative.

The frontal plane QRS axis exhibited a progressive rightward (inferior shift) from a mean of 55 at sea level to a maximum of 107 at 8,848 m ($p < 0.05$). Only a slight decrease in the axis toward normal occurred upon return to sea level (Figure 6).

The mean pulmonary artery pressure and pulmonary artery wedge pressure were 15 and 7 mm Hg, respectively, in 8 subjects at sea level. In 6 subjects at 6,100 m the mean pulmonary artery pressure was 24 mm Hg, in 2 subjects at 7,620 m it was 34 mm Hg and in 3 subjects at 8,848 m it was 24 mm Hg. The pulmonary artery wedge pressure remained unchanged at each altitude level. At each altitude pulmonary artery pressure became substantially more elevated during exercise, rising to 54 mm Hg at 7,620 m. Cardiac catheterization was not performed in all subjects at each altitude. Electrocardiograms were not recorded at the same time as the cardiac catheterization studies. Additional results of the hemodynamic studies have been published.⁹

The relation between the QRS axis, P-wave amplitude in inferior leads, S/R ratio in V₆ and the mean resting pulmonary artery pressure is shown in Figure 7. The electrocardiographic changes were maximal at 6,100 m and 8,848 m when the pulmonary artery pressure was highest.

No significant changes occurred in the QRS duration, PR interval, QT interval, T waves or ST segments on the resting electrocardiograms. No arrhythmias were noted and conduction defects did not occur.

Exercise electrocardiograms: Maximal exercise levels attained were 2.5 to 3.0 kpm at 7,620 m and 1.0 to 1.5 kpm at 8,848 m. These exercise levels are equivalent to an oxygen consumption of 25 and 16 ml/kg/min, respectively.

Mean resting heart rates before exercise were 110 ± 18 beats/min at 7,620 m and 105 ± 15 beats/min at 8,848 m. Heart rates during maximal exercise were 138 ± 7 and 19 ± 6 beats/min, respectively. These values correspond to approximately 75% of the maximal heart rates at sea level.

No ST depression, T-wave inversion or other ischemic changes were observed during any of the exercise tests. None of the subjects experienced any symptoms of myocardial ischemia. Dyspnea, general weakness and leg fatigue were the major symptoms requiring cessation of exercise. No arrhythmias were present on the resting electrocardiograms. One subject had isolated unifocal ventricular premature beats during submaximal exercise at 7,620 m. The contour of the premature beats suggested a left ventricular origin. Another subject had several multifocal left ventricular premature beats and a short run of bigeminal rhythm at the same amplitude (Figure 8). Another subject had occasional multifocal ventricular premature beats and a run of bigeminy at the same altitude and multifocal ventricular premature beats at 8,848 m. These complexes were of right ventricular origin. Postexercise electrocardiograms

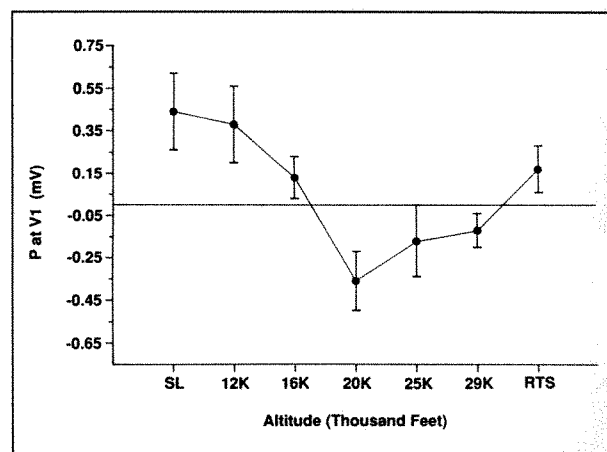


FIGURE 3. Amplitude of P waves in lead V₁ above and below isoelectric line at sea level and 5 altitudes. Abbreviations and symbols as in Figure 1.

commonly showed minor repolarization changes including QT prolongation with prominent U waves (5 subjects), prominent U waves alone (1 subject) and flat topped or notched T waves (2 subjects). In 3 subjects moderate ($+90$ to $+180^\circ$) right-axis deviation appeared and in 2 others extreme right-axis deviation appeared ($+180$ and $+270^\circ$) during exercise and reverted to the resting appearance when exercise ceased (Figure 9).

DISCUSSION

Most earlier studies of the electrocardiogram at high altitude have obtained results similar to ours.¹⁻⁷ During the American Medical Research Expedition to Mt. Everest, resting electrocardiograms were recorded in 12 subjects at sea level, 5,400 m and 6,300 m.⁶ At 6,300 m, 3 subjects developed right bundle branch block, and 3 developed a right ventricular hypertrophy pattern. Ventricular premature beats were seen in 1 subject and 1 exhibited atrial premature beats. No ST-segment changes were noted. All changes returned to control lev-

els after descent. Das et al⁷ reported similar electrocardiographic changes in 20 subjects transported rapidly from 195 m to 3,200 m and in 20 others transported to 3,771 m.

Previous workers have attributed most of the electrocardiographic changes at high altitude to the development of pulmonary hypertension.¹⁻⁷ The present study is the first in which pulmonary artery pressure was measured and related to electrocardiographic changes.⁹ Most of the changes observed, including those in heart rate, showed a clear relation to pulmonary artery pressure up to 7,620 m (Figure 7). The most likely explanation for the electrocardiographic changes is pulmonary hypertension that resulted in a transient right ventricular strain pattern similar to that seen at sea level in acute cor pulmonale due to pulmonary embolism.¹⁰ Echocardiographic observations in the same subjects revealed moderate right ventricular enlargement, paradoxical septal motion and well-preserved right ventricular systolic emptying at rest and during exercise.¹¹ An additional factor could be the development of a moder-

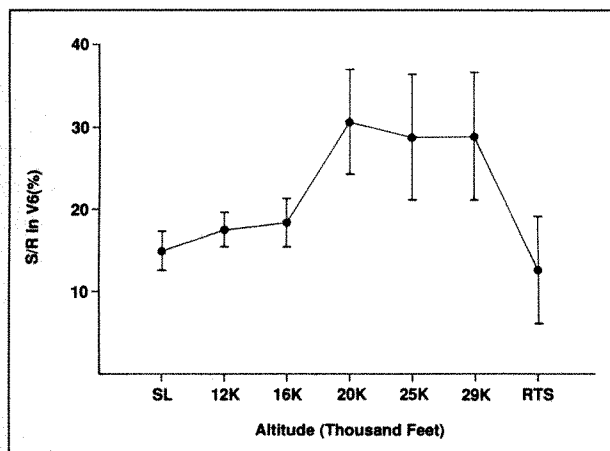


FIGURE 4. Ratio of S waves to R waves in lead V₆ at sea level and 5 altitudes. Abbreviations and symbols as in Figure 1.

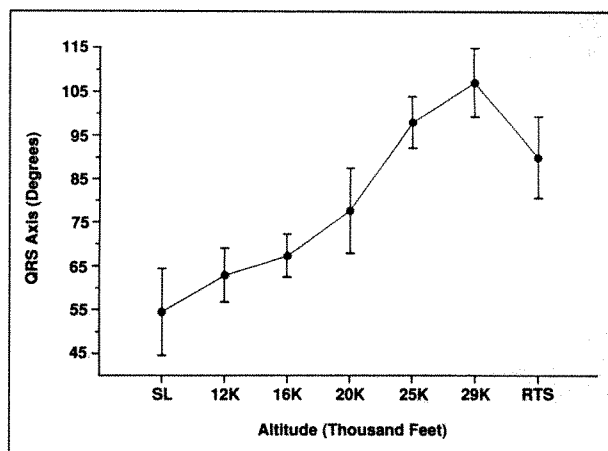


FIGURE 6. Frontal plane QRS axis in degrees at sea level and 5 altitudes. Abbreviations and symbols as in Figure 1.

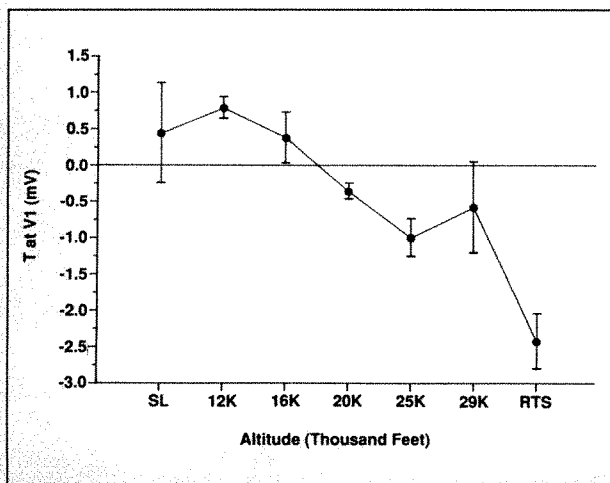


FIGURE 5. Amplitude of T wave in lead V₁ above and below the isoelectric line at sea level and 5 altitudes. Abbreviations and symbols as in Figure 1.

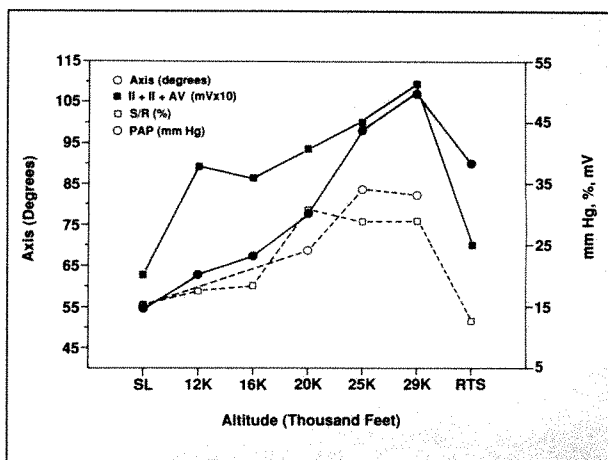


FIGURE 7. Frontal plane axis, sum of P-wave amplitude in leads II, III and aVF, ratio of S wave to R wave in lead V₆ and mean resting pulmonary artery pressure (PAP) at sea level and 5 altitudes. Abbreviations as in Figure 1.

ate degree of right ventricular hypertrophy. While most electrocardiographic changes in the present study reverted promptly to sea level values upon descent, right axis deviation, negative T waves in V_1 and low T waves in V_2 persisted. This suggests the presence of some degree of anatomic right ventricular hypertrophy. This is supported by echocardiographic observations in the same subjects indicating an increase in right ventricular dimensions.¹¹

Exercise electrocardiograms have not been previously performed at extreme altitudes except to determine heart rate and rhythm. An important observation of the present study was the absence of any ST- or T-wave changes indicating myocardial ischemia at rest or during maximal exercise at any altitude level including 8,848 m. At this altitude the mean resting arterial oxygen saturation was 58%. During exercise the measured arterial oxygen saturation was 51% with a pH of 8. An important factor that would minimize myocardial ischemia under these severe conditions is the fact that left ventricular work was considerably reduced compared to

sea level. At 8,848 m the maximal heart rate was only 75% of maximal sea level values and the mean arterial pressure was 90% of sea level values, indicating a significant decrease in double product and left ventricular work. In addition, echocardiographic studies of left ventricular function revealed no abnormalities and left ventricular dimensions were smaller at high altitude than at sea level both at rest and during exercise. This is compatible with the lower stroke volume and a lesser degree of cardiac work.¹¹

Part of the explanation for the lack of evidence of ischemia or left ventricular dysfunction under these conditions of severe hypoxemia is a lesser degree of cardiac work. This study, however, also indicates that oxygen delivery to the myocardium can be maintained at arterial oxygen saturations as low as 49%.

This is supported by Guenter¹² who studied 16 normal subjects who performed maximal exercise at sea level while breathing 10% oxygen in nitrogen. Despite a mean arterial PO_2 of 31 mm, no electrocardiographic evidence of ischemia was observed and no episodes of

FIGURE 8. Extreme right-axis deviation in a resting electrocardiogram at 282 torr (7,620 m).

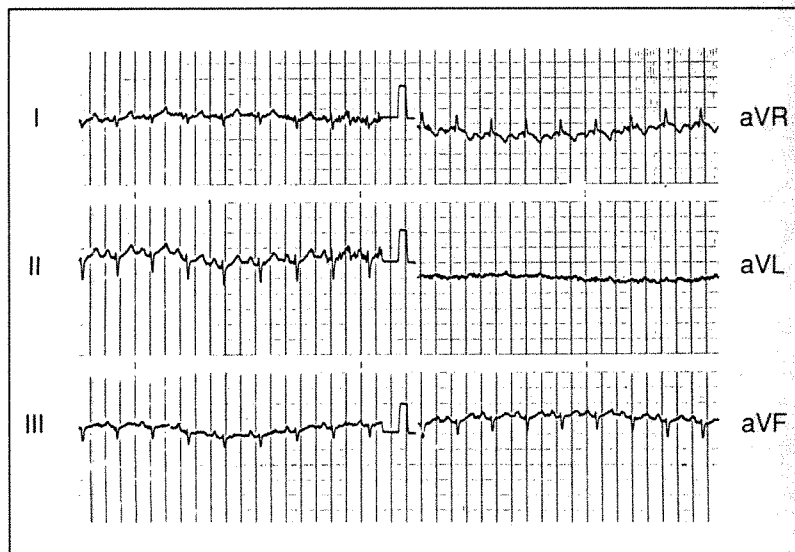


FIGURE 9. Ventricular premature beats in a bigeminal rhythm during exercise at 3 kp at 282 torr (7,620).



chest pain occurred. Ventricular premature beats occurred in 4 subjects during exercise but the arrhythmias were transient and benign. There were no runs or repetitive forms. Ventricular ectopy in young, asymptomatic subjects during exercise at sea level is considered benign.^{13,14}

Several minor methodologic problems and deficiencies should be noted. First, resting electrocardiograms were not recorded at the same time of day, and the subjects were not in a basal state. This may have accounted for the variations in resting heart rates. The duration of exercise at the highest workload in some subjects was <3 minutes, which suggests that steady state may not have been attained. Finally, only 3 subjects exercised at the highest altitude. These deficiencies do not affect the general conclusions that can be derived: electrocardiographic changes in normal young men exposed to extreme altitudes in a hypobaric chamber were similar to those observed in mountaineers and subjects transported to high altitudes. The changes are compatible with pulmonary hypertension, which was present in all subjects and was roughly proportional to the altitude. Electrocardiograms recorded during maximal exercise revealed no evidence of ischemia despite the presence of severe hypoxemia and indicated that under these conditions of stress myocardial oxygen delivery was not impaired.

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Thrombotic and Cardiovascular Complications Related to Nonionic Contrast Media During Cardiac Catheterization: Analysis of 8,517 Patients

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The incidence of major complications associated with nonionic contrast media has not been defined in a large study. Accordingly, cardiovascular complications, especially thrombotic events, were prospectively evaluated in 8,517 consecutive patients undergoing diagnostic cardiac catheterization with either iopamidol (n = 6,293) or iohexol (n = 2,224). Thrombotic events were defined as coronary embolus, coronary occlusion, transient ischemic attack or stroke occurring at the time of catheterization. Thrombotic events occurred in 15 patients (0.18%). Coronary thrombus or embolus occurred in 7 patients, a thromboembolus from the ventricular catheter occurred in 1 patient and transient ischemic attack or stroke occurred in 7 patients. Six of 15 patients with thrombotic events were premedicated with heparin. Thrombotic events were unusual in that they tended to occur in clusters within short time intervals. On 1 occasion, a thrombus was observed in the catheter tip before embolization. Other cardiovascular complications were similarly low with an incidence of ventricular tachycardia/fibrillation of 0.1%, profound bradycardia of 0.2% and prolonged angina of 0.3%. There were 2 deaths unrelated to thrombotic events. Although the clinical thrombotic events associated with nonionic contrast have an unusual temporal clustering and may result in major complications, the overall incidence (0.18%) of these thrombotic complications with nonionic contrast agents is quite similar to that reported with ionic contrast media.

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Major complications during cardiac catheterization, although often attributable to the procedure itself, may also result from the administration of contrast media.¹⁻⁵ In comparison to ionic contrast agents, nonionic contrast agents have been documented to decrease the incidence of major complications associated with cardiac catheterization.⁶⁻⁸ However, previous studies have been unable to define the true incidence of adverse cardiovascular and thrombotic events due to the limited number of patients described.

Nonionic contrast agents lack the anticoagulant activity of ionic contrast.^{9,10} Thrombosis possibly related to nonionic contrast has been suggested in a previous study from this laboratory,⁷ from observation of clot within injector syringes¹¹ and from reports of thrombosis on the tips of catheters themselves.¹² Due to less in vitro inhibitory effects of blood coagulation when compared to ionic contrast agents, the United States Food and Drug Administration has recently requested that package labelling of nonionic contrast be revised to include a warning regarding possible thrombosis. This study prospectively evaluates the incidence of thrombotic and major cardiovascular complications in a large consecutive series of patients undergoing diagnostic cardiac catheterization using nonionic contrast agents.

METHODS

Patient population: Eight thousand five-hundred and seventeen consecutive patients undergoing diagnostic cardiac catheterization at Duke University Medical Center were prospectively enrolled into the study between April 1, 1987 and April 27, 1989. Eleven hundred forty-four of the current study group were previously reported in a separate publication that described the cardiovascular and nephrotoxic effects of nonionic contrast within 24 hours after cardiac catheterization.⁵ Patients with acute evolving myocardial infarction and those having percutaneous transluminal coronary angioplasty were excluded. Before the procedure, demographic data, medical history and physical examination were recorded and entered into a computerized medical system.¹³

The indication for cardiac catheterization was a history of chest pain in 7,349 (86%) patients or a history of valvular heart disease in 1,168 (14%) patients. In patients with valvular disease, mitral stenosis was present in 162 (14%), aortic stenosis in 396 (34%), mitral regurgitation in 575 (49%), aortic regurgitation in 543

(46%), pulmonic stenosis in 5 (0.4%), tricuspid regurgitation in 43 (0.3%), tricuspid stenosis in 1 (0.1%) and pulmonic regurgitation in 4 (0.3%).

Cardiac catheterization: After premedication with 25 to 50 mg of diphenhydramine hydrochloride intravenously, diagnostic cardiac catheterization was performed via the percutaneous femoral route in 99% of patients and by the percutaneous brachial route in the remainder. If a previous history of an allergic reaction to contrast media existed, the patient was also premedicated with methylprednisolone and cimetidine. Iopamidol (Isovue—370, Squibb Inc.) was used in the first 6,293 (74%) patients, whereas iohexol (Omnipaque—350, Winthrop Pharmaceuticals) was used in the subsequent 2,224 (26%) patients.

Left ventriculography was performed either biplane or single plane using 40 to 45 cc of contrast at 12 to 15 cc/s. Selective coronary arteriography was done in multiple views with either 5-, 6 or 7Fr catheters. During the procedure, a technician or nurse recorded a detailed account of the protocol including medications administered and any complication that occurred. The report was then verified by the cardiology fellow and the attending physician performing the procedure. If a major complication occurred, the cineangiogram and the hospital record were reviewed by 2 investigators (CJD, TMB) to further define the circumstances of the adverse event.

Definitions: For purposes of this study, only patients with major complications attributable to the procedure were analyzed. Sustained ventricular tachycardia was defined as ventricular tachycardia that required cardioversion, produced syncope or was ≥ 30 seconds in duration. Profound bradycardia was defined as a heart rate < 40 beats/min that lasted > 10 seconds or did not respond to cough. Prolonged angina was defined as typical chest pain symptoms that persisted ≥ 15 minutes and required nitroglycerin, calcium antagonist or morphine sulfate, or were associated with reversible electrocardiographic changes.

Thrombotic events were defined as coronary occlusion, coronary embolus, transient neurologic ischemic attack or stroke occurring during the procedure. Coronary embolus was defined as a thrombus which was seen to be emitted from the catheter tip. Coronary dissection and other nonthrombotic coronary occlusion were excluded.

Data analysis: The data for continuous variables are expressed as mean $\pm$ standard deviation. Percentages and/or the number of patients with a characteristic are used to report the data for discrete variables. Due to the small number of thrombotic events, Fisher's exact test was used to test the difference in the occurrence of these events for risk groups and for the type of contrast media administered.

RESULTS

The demographic characteristics of the study group are listed in Table I. The mean age was 59 ± 12 years with 1,374 (16%) patients > 70 years. Three-vessel and/

or left main coronary artery disease was present in 1,911 (22%) patients. The mean ejection fraction was 52 ± 13 , with 1,399 (17%) of the patients having an ejection fraction $< 40\%$.

Table II lists the incidence of thrombotic and cardiovascular nonthrombotic adverse reactions that occurred during cardiac catheterization. There was no significant difference in thrombotic events for the 2 contrast agents (iopamidol; 11 of 6,293 patients [0.17%] vs iohexol; 4 of 2,224 patients [0.18%], $p = 1.00$). Patients undergoing catheterization for valvular heart disease had a 0.17% incidence of thrombotic complications. Similarly, those in which the procedure was indicated for chest pain had an incidence of 0.18% ($p = 1.00$).

The incidence of nonthrombotic cardiovascular adverse events was 0.5 and 1.0% for patients in which the procedure was indicated for chest pain and valvular disease, respectively. There was no significant difference in the incidence of nonthrombotic cardiovascular complications in patients with aortic stenosis (0.76%) versus those with suspected coronary artery disease (0.46%); $p = 0.44$.

Of the 15 patients who developed any thrombotic event (i.e., coronary or neurologic), 6 (40%) were premedicated with heparin and 8 received prior aspirin. In the total cohort, intravenous heparin (3,000 to 5,000 units) was administered after arterial access in 41% of patients and 53% of patients were receiving aspirin before catheterization.

The episodes of thrombosis appeared to occur in clusters. During 1 grouping, 2 occurred on the same day, on another occasion, 2 occurred within 10 days and in a third grouping, 2 occurred within 5 days. This was noted despite different contrast media manufacturer's lot numbers. An extensive evaluation of other factors, such as types of catheters, wires, procedures, flush solutions, individuals involved in performing the procedure and temperature of the contrast, failed to reveal any obvious precipitating factor that explained the clustering nature of these events. There was no relation established between these events and the use of heparin therapy, although, as noted above, systemic heparinization is not routine in all cases.

On at least 1 occasion, a catheter was observed, in retrospect, to have thrombus attached to the catheter tip before embolization into the coronary artery. On another occasion, a "worm-like" thrombus was observed to be ejected out of the distal end of a pigtail catheter during left ventriculography.

There were 6 episodes of coronary occlusion and 1 episode of coronary embolus. Four of 7 patients were premedicated with intravenous heparin (2,000 to 3,000 units) and 3 with aspirin. Two patients were free of significant coronary artery narrowing before the adverse event. Three patients were treated successfully with percutaneous transluminal coronary angioplasty, 2 of whom also received intracoronary streptokinase. However, 3 patients required emergent coronary artery bypass surgery due to failure of intracoronary thrombolytic therapy and/or coronary angioplasty to maintain ves-

TABLE I Patient Demographics

	n	(%)
Age >70 yrs	1,374	(16)
Men	5,457	(64)
History		
Diabetes mellitus	1,480	(19)
Congestive heart failure	1,843	(23)
Peripheral vascular disease	864	(11)
Cerebrovascular disease	640	(8)
Systemic hypertension	4,066	(50)
Prior myocardial infarction	3,909	(46)
Coronary artery bypass surgery	827	(10)
Angiographic data		
Significant coronary artery narrowing	5,443	(64)
3 coronary arteries significantly narrowed	1,852	(22)
Left main significantly narrowed	334	(4)
Ejection fraction <40%	1,399	(17)

Percentages based on total available number of observations per variable.

sel patency. In 1 patient, thrombus embolized to the distal left anterior descending artery without sequelae.

There were 2 deaths, unrelated to the use of contrast media (0.02%). One occurred in a patient with 3-vessel coronary artery disease who presented with unstable angina, uncontrolled on medical therapy, and who underwent coronary artery bypass grafting. She developed electromechanical dissociation and died. The second death occurred in a patient who had incurred a recent non Q-wave myocardial infarction and recurrent ischemia. Catheterization revealed 3-vessel coronary artery disease. Occlusion not due to embolization of the right coronary artery occurred in the region of an obvious coronary thrombus that was the cause of the patient's original clinical presentation. Despite angiographically successful angioplasty, the patient developed electromechanical dissociation and died.

DISCUSSION

This study verifies the low incidence of major cardiovascular complications that occur with the use of non-ionic contrast agents during cardiac catheterization. Previously published retrospective data from our laboratory describing a separate cohort of patients have shown about a 3-fold decrease in major complications when nonionic replaced ionic contrast media in this setting.⁷

The current study prospectively evaluated the incidence of adverse events, especially thrombotic events, in a large consecutive group of patients undergoing diagnostic cardiac catheterization with nonionic contrast. Thrombotic complications were noted in 0.18% of patients. A previous retrospective study from this laboratory using ionic contrast in 2,650 patients showed a 0.15% incidence of stroke and acute myocardial infarction.⁷ Data on 53,581 patients from the Registry Committee of the Society of Cardiac Angiography reported that acute myocardial infarction and stroke occurred in 0.14% when ionic contrast was used.¹⁴ Similarly, the Coronary Artery Surgery Study reported a 0.22% incidence of myocardial infarction and stroke.¹ Although thrombotic events with nonionic contrast media appear to be unusual in that some occurred within a short time

TABLE II Thrombotic and Nonthrombotic Cardiovascular Events Occurring During Cardiac Catheterization with Nonionic Contrast Media

	No. of Patients	Coronary Occlusion	Coronary Embolus	LV Catheter Thrombus	TIA	Stroke
Thrombotic events						
Iopamidol	6,293	5	0	1	2	3
Iohexol	2,224	1	1	0	0	2
Total	8,517	6	1	1	2	5
	No. of Patients	Prolonged Pain	VT/VF	Profound Bradycardia		
Cardiovascular events						
Iopamidol	6,293	14	2	5		
Iohexol	2,224	15	3	10		
Total	8,517	29	5	15		

LV = left ventricular; TIA = transient ischemic attack; VF = ventricular fibrillation; VT = ventricular tachycardia.

LV = left ventricular; TIA = transient ischemic attack; VF = ventricular fibrillation; VT = ventricular tachycardia.

interval and actual thrombus was observed on a catheter tip in 1, the overall incidence compares favorably with these previous reports using ionic contrast agents.^{1,7,14}

It cannot be stated with certainty that the thrombotic events, especially neurologic, are directly related to the contrast media used. Other mitigating circumstances, including endothelial and plaque trauma with catheters or guidewires, may provide an adequate nidus for thrombus formation, plaque disruption or thromboembolism.

Hwang et al¹⁵ have suggested that nonionic contrast agents have fewer inhibitory effects on blood clot formation and might be associated with a higher risk of thromboembolic complications. Further, they imply that heparin inhibits clotting in the presence of nonionic medium. We could show no beneficial effect of prior heparinization in preventing thrombotic complications, although the doses of heparin that were used might be inadequate to affect this adverse reaction. Thus, heparin administered in doses of 3,000 to 5,000 units does not appear to affect the propensity for thrombus formation during cardiac catheterization. It appears likely that the mechanism responsible for clot formation with nonionic contrast involves more than a simple effect on the coagulation cascade. Thrombosis with nonionic agents could potentially involve platelet and fibrinogen interactions that would be relatively unaffected by anticoagulants such as heparin. Robertson¹¹ has also suggested adding heparin to the contrast medium. However, based on the overall incidence of thrombosis and the lack of observed effect of premedication with heparin, the validity of this approach could not be established. Whether nonionic contrast itself is a trigger for clot formation is unknown.

Major procedural complications were not related to the indication for catheterization. Patients with valvular and coronary disease experienced a near equal risk of thrombotic and nonthrombotic cardiovascular and adverse events.

This study, representing the largest prospective evaluation of complications associated with nonionic contrast used during cardiac catheterization, confirms the low incidence of thrombotic and nonthrombotic cardiovascular events.

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Comparison with Radionuclide Angiography of Two New Geometric and Four Nongeometric Models for Echocardiographic Estimation of Left Ventricular Ejection Fraction Using Segmental Wall Motion Scoring

Robert D. Rifkin, MD, and Hitoshi Koito, MD

Two new echocardiographic methods for estimating left ventricular ejection fraction, both based on segmental wall motion scoring on a continuous scale, were developed and compared to radionuclide angiography in 50 patients. The first method used a geometric model in which the ventricle was represented by a tubular base section joined to a hemielliptical apex section, each containing 4 quadrants. Contraction was scored visually in 12 regions of the ventricle. The 12 scores were converted to dimensional shortenings, which were then used to calculate separate ejection fractions for each of the 8 quadrants. These 8 values were averaged to obtain the global ejection fraction. Assuming an elliptical end-systolic cross-section shape for each quadrant, the correlation between the echocardiographic and radionuclide ejection fractions was 0.917 with a regression slope of 0.93 and an intercept of 1.5. Results were identical assuming circular end-systolic quadrant shapes.

The second approach used a linear combination of the mean wall motion score at the base, midleft ventricle and apex to predict ejection fraction. Coefficients for the 3 mean scores were optimized by least squares best fit with radionuclide ejection fraction in all 50 patients. The simplest linear model showed a correlation of 0.90 between the echocardiographic and radionuclide ejection fraction but underestimated low, and overestimated high, ejection fractions. However, these systematic errors could be removed by regression, which added a constant term of 8.1 and a slope factor of 0.87 to the linear model, improving the correlation with radionuclide ejection fraction to 0.91.

Segmental wall motion scoring on a continuous scale with an appropriate geometric model can provide good estimates of ejection fraction if each ventricular quadrant is analyzed separately and the results are averaged. Properly weighted linear combinations of the contraction scores provide comparably accurate estimates of the ejection fraction.

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Despite its dependence on both preload and afterload, the ejection fraction continues to be the most widely used clinical index of ventricular performance. Although 2-dimensional echocardiography excels in evaluating regional left ventricular function, it has not been as effective for estimating global ejection fraction.¹ Experienced observers report that a gross visual estimate of ejection fraction is as good as, or superior to, planimetry^{2,3} but the accuracy of this approach has not been confirmed in routine use. Moreover, since no theoretic rationale has been offered, it remains an unscientific method.

Previous work⁴ has shown that segmental wall motion scoring along a continuous scale can provide good estimates of the ejection fraction when used in conjunction with a geometric model that has 2 important features: first, the end-systolic cross-sections of the ventricle have elliptical shapes and second, each quadrant of the ventricle is considered independently; quadrants therefore may have different shapes to represent multiple regional wall motion abnormalities. However, since this model is computationally cumbersome, we examined 2 simpler approaches: a geometric model in which cross-sectional shape is circular rather than elliptical and nongeometric models that use a linear combination of segmental contraction scores as a prediction instrument. The purpose of this study was to compare these alternative models to radionuclide angiography, and to the previously described model.⁴

METHODS

Description of the geometric models: The ventricle was modelled by a tubular base section of length L_B joined to a hemielliptical apex section of length L_A (Figure 1). Both sections are divided into 4 quadrants. R_{1B} and R_{2B} represent the cross-sectional dimensions of a base quadrant and are assumed to be constant along its length. The cross-sectional radii of the apex quadrants taper elliptically, from maximum values of R_{1A} and R_{2A} at the junction with the base, to 0 at the apex. R_{1A}

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and $R2_A$ are the formal hemiaxial dimensions of the hemiellipse.

End-systolic and end-diastolic cross-sectional shapes: End-systolic cross sectional shape of the apex and base sections was assumed to be either elliptical (model I) or circular (model II). In both models, the radial dimensions of the 8 quadrants may differ to allow for representation of multiple wall motion abnormalities (Figure 2).

At end-diastole, it is assumed in both models I and II that all cross sections are circular (Figure 2) and that the volumes and cross-sectional radius, R , of the base and apex sections are equal. Thus, each section volume is $(\pi/S) \cdot R^2 \cdot L$, where $L = L_B$ or L_A , and $S = 1$ for the base, or $2/3$ for the apex section due to its elliptical tapering. Setting base and apex volumes and their radial dimension equal, $L_B = 2/3 \cdot L_A$. Thus, in both models, the base represents the proximal 40% of ventricular length and the apex section the distal 60%.

Ejection fraction of each quadrant: The ejection fraction of each quadrant is given by $(V_{ED} - V_{ES})/V_{ED} = 1 - (V_{ES}/V_{ED})$ where V_{ED} and V_{ES} are the end-diastolic and end-systolic volumes. Since $V = (\pi/S) \cdot R1 \cdot R2 \cdot L$, the ejection fraction of each base or apex quadrant is given by $1 - (R1_{ES}/R1_{ED}) \cdot (R2_{ES}/R2_{ED}) \cdot (L_{ES}/L_{ED})$. Substituting $K_{R1} = R1_{ES}/R1_{ED}$, $K_{R2} = R2_{ES}/R2_{ED}$ and $K_L = L_{ES}/L_{ED}$ leads to ejection fraction $= 1 - K_{R1} \cdot K_{R2} \cdot K_L$ for model I and ejection fraction $= 1 - K_{R^2} \cdot K_L$ for model II. It assumed in both model I and model II that the entire reduction in ventricular length due to contraction is represented as a change in length of the apex section only. Thus, for a base quadrant, $L_{ES} = L_{ED}$ and $K_L = 1$. Accordingly, in model I, ejection fraction $= 1 - K_{R1} \cdot K_{R2}$ for each base quadrant. Similarly, in model II, ejection fraction $= 1 - K_{R^2}$ for base quadrants.

Grading of segmental contraction in terms of contraction scores: Segmental contraction was evaluated visually from routine videotape recordings in the regions of the left ventricle that correspond to the previously defined radial and axial dimensions of the base and apex sections. Rather than estimate the value of K directly, wall motion was scored in each segment on a continuous scale in which normal contraction = 100, akinesis = 0, various degrees of hypokinesis are represented by wall motion scores between 0 and 100, and

dyskinesis and hyperkinesis are represented by scores below 0 and over 100, respectively. Generally, mild, moderate and severe hypokinesis are represented by scores of 75, 50 and 25, respectively, and mild and moderate hyperkinesis or dyskinesis by scores of 125 and 150 or -25 and -50, respectively. If contraction of a segment was nonuniform along its length, an average value was estimated and used as the score for the entire segment.

The value of each factor, K , was then calculated from its associated contraction score, C , by the relation $K = 1 - (C \cdot NLFS/100)$ where $NLFS$ is the normal systolic fractional shortening (defined as $1 - ESD/EDD$) of that dimension. Normal fractional shortening of myocardial segments varies slightly from region to region⁵ but a value of 0.35 is generally suitable for all radial dimensions.⁵ The normal lengthwise fractional shortening of the apex section becomes 0.42⁵ due to the assumption that all lengthwise shortening of the ventricle takes place in the apex section, which constitutes 60% of the total ventricular length. However, for computational simplicity, we assumed the apical fractional shortening was also 0.35. Thus, for model I: $EF_{base\ quadrant} = 1 - (1 - C_{R1-B} \cdot 0.0035) \cdot (1 - C_{R2-B} \cdot 0.0035)$ and $EF_{apex\ quadrant} = 1 - (1 - C_{R1-A} \cdot 0.0035) \cdot (1 - C_{R2-A} \cdot 0.0035) \cdot (1 - C_{L-A} \cdot 0.0035)$ where C_{R1-B} , C_{R2-B} , C_{R1-A} , C_{R2-A} , and C_{L-A} are the contraction scores of the 2 base quadrant radii, the 2 apex quadrant radii, and the score for the lengthwise contraction of the apex, respectively. For model II, since the radial dimensions of each quadrant are assumed to be equal: $EF_{base\ quadrant} = 1 - (1 - C_{R-B} \cdot 0.0035)^2$, and $EF_{apex\ quadrant} = 1 - (1 - C_{R-A} \cdot 0.0035)^2 \cdot (1 - C_{L-A} \cdot 0.0035)$.

In both models I and II, each base quadrant is assigned 1 contraction score, representing the radial contraction of the entire basal 40% of the ventricle in that quadrant. Each apex quadrant receives 2 scores, one for radial contraction of the midventricular region just distal to the base section, and one for the lengthwise contraction of the apex. Thus, 4 scores are needed to describe contraction around the circumference of the ventricle at the base, 4 for the middle of the ventricle and 4 for the apex, for a total of 12 contraction scores.

Global ventricular ejection fraction: Global ejection fraction was obtained as the mean of the ejection fractions of the 8 quadrants. We assumed equal end-diastol-

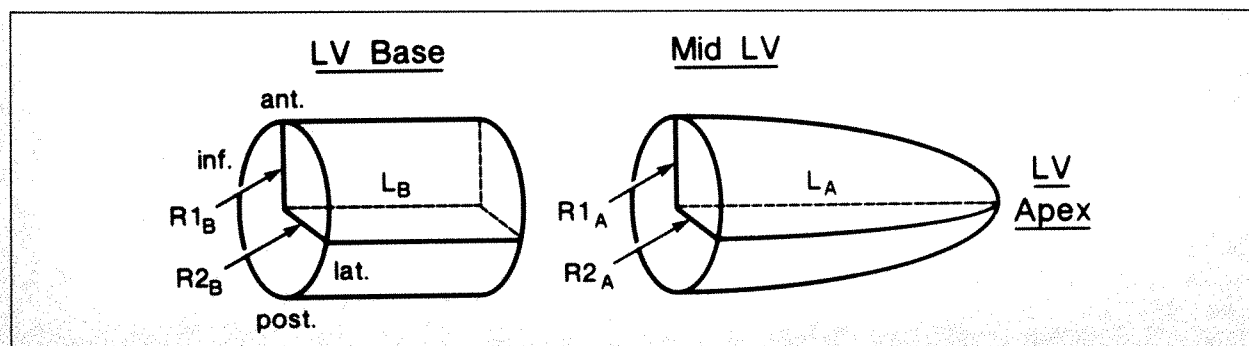


FIGURE 1. Tubular-shaped base representing the proximal left ventricle (LV) and hemielliptical apex representing the distal LV. A circular cross-sectional shape has been drawn, but end-systolic cross sections may be elliptical or circular (see Figure 2). Two of the 8 quadrants are illustrated.

ic volumes of all 8 quadrants. Thus, ejection fraction = $\sum_n (EF_{Bn} + EF_{An})/8$, where n indexes the 4 quadrants in each section ($n = 1$ to 4), and EF_{Bn} and EF_{An} are the ejection fractions of the base and apex quadrants, respectively. Comparisons of global ejection fraction by this method with radionuclide angiography are shown in Table I and Figure 3.

Nongeometric models for global ejection fraction:

In models III through VI, we examined the use of linear combinations of the contraction scores as instruments for predicting ejection fraction. These were of the form: $X_{\text{model}} = B0 + B1 \cdot \bar{C}_{\text{base}} + B2 \cdot \bar{C}_{\text{mid-LV}} + B3 \cdot \bar{C}_{\text{apex}}$ where $\bar{C}$ is the mean of the 4 contraction scores at the base, the midleft ventricle and the apex, respectively.

In model III, the coefficients $B0$, $B1$, $B2$ and $B3$ of $X_{\text{model III}}$ were determined by finding the least squares best fit between the linear combination of contraction scores and the radionuclide ejection fraction for all 50 patients, subject to the constraint that the predicted ejection fraction is zero when all contraction scores are zero. This constraint forces the constant, $B0$, to take a value of zero. The coefficients are listed in Table II. Figure 4 shows the values predicted by model III for all 50 patients plotted on the x axis versus the corresponding radionuclide angiogram ejection fractions on the y axis. Line 1, $Y = X$, represents the assumption that the actual ejection fraction is directly equal to the raw value given by $X_{\text{model III}}$, that is, ejection fraction = $X_{\text{model III}}$. Although line 1 is not a true regression line, to characterize how well this assumption fits the data, we calculated a correlation coefficient for it using the deviations of the radionuclide ejection fraction from this line, $EF_{\text{RNA}} - X_{\text{model III}}$, for each case.

In model IV, we determined a formal regression line between the values given by $X_{\text{model III}}$ and the radionuclide angiogram ejection fractions. This represents the assumption that ejection fraction = $m \times (X_{\text{model III}}) + b$ and it is depicted by line 2 in Figure 4. The coefficients of model IV were obtained by transforming model III according to the values of the parameters, b and m as

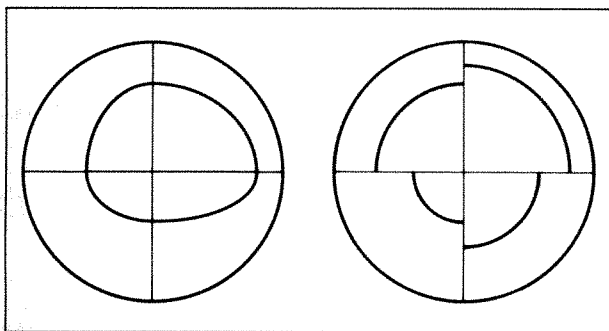


FIGURE 2. Cross-sectional view of model I (left) and model II showing how the models differ in their representation of the end-systolic shape of each quadrant. *Outer lines* represent endocardium at end-diastole, which is assumed to be circular in both models. *Inner lines* represent end-systolic position. Significant variation in the wall motion of each of the 4 quadrants is illustrated. In model I, the 2 radii of each quadrant can be unequal at end-systole, whereas in model II they are always equal. Conversely, the radial dimension shared by adjacent quadrants is always equal in model I but is unequal at end-systole in model II.

follows: $X_{\text{model IV}} = b + (m \cdot B1) \cdot \bar{C}_{\text{base}} + (m \cdot B2) \cdot \bar{C}_{\text{mid-LV}} + (m \cdot B3) \cdot \bar{C}_{\text{apex}}$.

Models V and VI represent ad hoc modifications of the coefficients of models III and IV, arrived at subjectively by inspection of Figure 4. The coefficients were selected to improve accuracy for ejection fractions between 15 and 35% and to simplify the equations for easy recall of the coefficients.

Study population: We selected consecutive echocardiograms retrospectively from studies performed in the clinical laboratory in patients who had radionuclide angiography within 7 days. The degree of inhomogeneity of segmental wall motion was characterized by calculating the variance⁶ of the 12 wall motion contraction scores in each patient.

Radionuclide angiography: Radionuclide angiography was performed in a standard manner. Ejection fraction was measured as the fractional change in diastolic and systolic counts in the region of interest after background subtraction.

Statistical methods: The correlation coefficients, standard errors of the estimate, variances and multiple linear regression coefficients were determined by conventional methods.⁶

RESULTS

Population: Fifty of 54 patients with echocardiograms and radionuclide scans performed within 7 days of each other had adequate image quality for wall motion analysis. Thirty-two were men and 18 were women. Average age was 67 ± 14 years (range 21 to 92). Radionuclide ejection fractions ranged from 10 to 85%. Coronary artery disease was present in 21, cardiomyopathy in 8, left ventricular hypertrophy in 15, aortic ste-

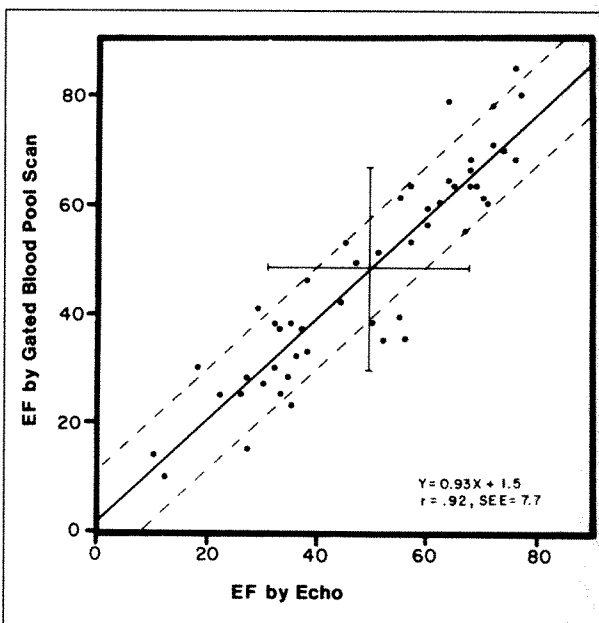


FIGURE 3. Correlation between the ejection fraction (EF) by echocardiography using model I and radionuclide angiogram in all 50 patients studied. The *solid line* is the line of regression, the *dashed lines* represent 1 standard error of the estimate, and the *cross-hatches* show the mean values and 1 standard deviation of the variates.

TABLE I Agreement Between Ejection Fraction by Radionuclide Angiography and Echocardiography Using Geometric Models

Model	Cross-Section	No.	EF*		Regression Coefficients†			SEE
			Echo	RNA	m	b	r	
I	Elliptic	50	49.1 ± 18.7	47.4 ± 19.0	0.93	1.5	0.917	7.68
II	Circular	50	48.5 ± 18.9	47.4 ± 19.0	0.93	2.5	0.918	7.67

* Mean ± standard deviation.

† $EF_{RNA} = m \cdot (EF_{echo}) + b$.

Echo = echocardiography; EF = ejection fraction; r = correlation coefficient; RNA = radionuclide angiography; SEE = standard error of the estimate.

nosis in 6, mitral regurgitation in 5 and aortic insufficiency in 4. Three patients had no evidence of heart disease.

Wall motion scores: Eight patients had dyskinetic wall motion in at least 1 segment. Twenty patients had at least 1 segment with a score <20 and also had at least 1 segment with a score >80. The median degree of variation in segmental wall motion in the population, based on the variance of the 12 contraction scores in each case, was represented by a patient with scores of 70, 100, 90 and 100 in the base segments, 70, 100, 75 and 85 in the midventricle and 50 in all 4 apex segments. The patient with the most inhomogeneous contraction in this study had base scores of 100, 110, 75 and 70, midventricular scores of 65, 100, 35 and 30, and apex scores of -25, 0, 0 and -30.

Geometric models: Regression analysis of the echocardiographic and radionuclide ejection fraction for

model I yielded a correlation coefficient of 0.917, standard error of 7.68, regression line slope of 0.93 and intercept of 1.5 (Figure 3 and Table I). Thus, the raw predicted ejection fractions with model I will slightly underestimate the low, and slightly overestimate the high, ejection fractions but the deviations are not enough to require routine correction by the regression coefficients. Correlation between the raw values predicted by model I before regression and the radionuclide values was 0.911.

Previous work⁴ demonstrated that with model I, the correlation between echocardiographic and radionuclide angiogram ejection fraction was as good in the 25 patients with the most inhomogeneous wall motion as in the 25 with the most uniform wall motion. Furthermore, this model performed equally well in those with low and high radionuclide angiogram ejection fractions.⁴ Table I shows that, when compared to the radionuclide angiogram ejection fractions, the accuracy of the circular and elliptical models is almost identical. The correlation coefficient between these 2 geometric models exceeded 0.99 with a standard error of the estimate of 0.62, a regression slope of 0.99 and an intercept of 1.0.

Linear models: Ideally, a model should predict an ejection fraction of zero when all contraction scores are zero and an ejection fraction around 65% when all scores are 100. However, due to the nonlinear relation between changes in the dimensions and the volume of ellipses and cylinders, this requirement cannot be totally satisfied in a linear model (Table II). Thus, model III (line 1, Figure 4) demonstrates a greater tendency toward underestimation of low ejection fractions and overestimation of high ejection fractions than models I and II and has a correlation coefficient of 0.896 with the radionuclide angiogram ejection fraction. However, the deviations were largely corrected by regression of the values predicted by model III against the radionuclide angiogram ejection fraction. This is seen in model IV (line 2, Figure 4) in which the parameters of model III were modified according to the regression coefficients. An improved agreement between the predicted echocardiographic and radionuclide angiogram ejection fraction is obtained (Table II) with a correlation coefficient of 0.914, which is almost the same as the geometric models.

Models V and VI demonstrate the effect of ad hoc modifications of the prediction equation. Inspection of Figure 4 shows that the simple addition of a constant term, $B_0 = 4$, to model III (line 3, Figure 4) improves

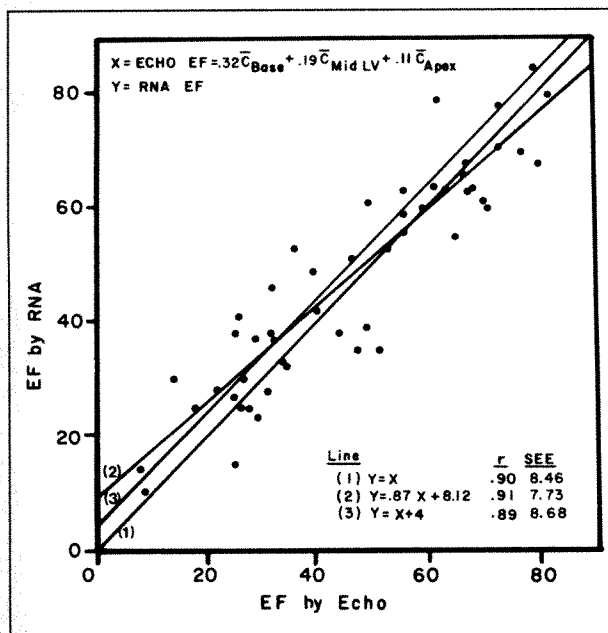


FIGURE 4. Relation between the ejection fraction (EF) by echocardiography (Echo) using a linear model and EF by radionuclide angiogram (RNA). The points are the values predicted by the linear combination shown on the graph (model III) in the 50 patients studied, based on the segmental contraction scores. Line 1 ($y = x$), representing the assumption that model III directly predicts the EF, shows slight underestimation of the low and overestimation of the high EF. This is corrected by line 2 (model IV). Line 3 (model V), obtained by simply adding a constant to line 1, agrees closely with line 2 for EF between 15 and 45%, but overestimates high EF.

TABLE II Agreement Between Ejection Fraction Predicted by Linear Combinations of the Contraction Scores and Radionuclide Angiography

Model	Prediction Coefficients*				No.	EF [†]		Correlation with RNA EF	
	B0	B1	B2	B3		Echo	RNA	r	SEE
III	0	0.32	0.19	0.11	50	45.4 ± 20.2	47.4 ± 19.0	0.896	8.46
IV	8.1	0.28	0.16	0.10	50	47.4 ± 17.5	47.4 ± 19.0	0.914	7.73
V	4	0.32	0.19	0.11	50	49.4 ± 20.2	47.4 ± 19.0	0.890	8.68
VI	4	0.30	0.20	0.10	50	48.0 ± 19.6	47.4 ± 19.0	0.909	7.94

* $EF_{echo} = B0 + B1 \cdot \bar{C}_{base} + B2 \cdot \bar{C}_{mid-LV} + B3 \cdot \bar{C}_{apex}$, where $\bar{C}$ = mean of the 4 contraction scores at that level of the ventricle.
† Mean ± standard deviation.
Abbreviations as in Table I.

the visual agreement between the values predicted by echocardiogram and radionuclide angiogram in the important range of ejection fractions between 15 and 35%. This improvement comes at the expense of increased overestimation of high ejection fractions, resulting in a slight deterioration in the correlation coefficient, which fell to 0.890. In practice, however, the addition of the constant could be restricted to cases in which the ejection fraction predicted by model III is <40. Finally, the parameters in model VI have been selected for simplicity and easy recollection, based on the values found to be accurate in models IV and V. The correlation coefficient of 0.909 and standard error of 7.94 are closer to those of the optimized linear combination of model IV.

DISCUSSION

Regional wall motion scoring indexes have been shown to be useful in the risk stratification of acute and early postmyocardial infarction patients.⁷⁻¹⁶ In this setting, the prognostic accuracy of such indexes is comparable to that of the left ventricular ejection fraction determined by radionuclide⁷ and contrast⁸ angiography, suggesting that a direct and clinically useful relation between simple wall motion scoring and global left ventricular ejection fraction exists. Yet only 1 study⁷ has compared index scores directly to the global ejection fraction and reported a correlation coefficient of only 0.55. However, the segmental scoring scale used in this study was discontinuous, arbitrary and unintuitive and the myocardial segment boundaries were not based on any geometric model. Moreover, a simple summation of all the segment scores was used for estimation of the global ejection fraction rather than a least squares best fit methodology. Thus all segments received the same weight in the total score. Finally contrast angiography, rather than radionuclide angiography, was the reference method. These factors probably account for the poor correlation coefficient.

Our study demonstrates that wall motion scores can be translated into accurate estimates of ejection fraction by geometric models and by simple linear combinations of the wall motion scores when the latter are based on appropriate geometric assumptions with proper weight given to the contribution of each segment. The results also indicate that a geometric model with circular cross-sections in each quadrant appears to be as accurate as one with elliptical cross-sections despite its relative simplicity. Although geometric models may have a slightly

greater accuracy than linear models, it is probably not enough to justify their additional computational complexity. Geometric models may still prove to be significantly superior to linear models in ventricles with marked dyssynergy, which were a small fraction of our study population. However, cases with significantly inhomogenous segmental function were well represented in this study population and, therefore, our findings are valid for the spectrum of cases routinely seen in the clinical laboratory of a secondary referral center.

The relative magnitude of the 3 coefficients in the linear models indicates that the contraction of the basal left ventricle is a slightly more important determinant of global ejection fraction than midleft ventricular contraction, and the apex is least important. However, it must be emphasized that the coefficient values depend on the geometric definition of the segments, particularly the relative lengths of the base and apex sections, and to some extent on the mixture of ventricles studied. It also appears necessary to include a constant term in the linear combination to remove systematic underestimation of low ejection fractions. This constant produces a non-zero ejection fraction for mean contraction scores of zero; therefore, for scores very near zero, it must cause overestimation. However, this appears to occur only at values so low as to be incompatible with survival.

The models described here have several advantages over previous nonplanimetric approaches. In contrast to the method of Baran et al,¹⁶ the present methods incorporate the function of all myocardial segments in the estimate of ejection fraction. Visual estimation of wall motion, rather than measurement as used in these past studies,^{16,17} avoids the loss of endocardial definition that occurs in static images. However, measurements can be used with the present method in some segments if desired.⁴

In addition to these advantages, the linear models lead to a simplified scheme for estimating left ventricular ejection fraction. For example, using model VI, it is apparent that a change in contraction score for any single base quadrant from 100 to 0 results in a decline in the global left ventricular ejection fraction of 7.5 percentage points. If mild, moderate and severe hypokinesis is associated with contraction scores of 75, 50 and 25, then each category decline in function of a single quadrant results in a fall in global left ventricular ejection fraction of 7.5/4 or 1.875 points for a base quadrant, 1.25 points for the midleft ventricle and 0.625 points for

the apex. Starting with a normal ejection fraction of 65%, points can be subtracted on a segment-by-segment basis according to this scheme to arrive at the final estimate. For example, total akinesis of the apex causes overall left ventricular ejection fraction to decrease from 64 to 54%.

The accuracy of the linear models explains the success of the "educated guess"^{2,3} of the left ventricular ejection fraction. With experience, observers probably develop an intuitive sense of the linear relations and coefficients. Accordingly, these models may expedite learning to make accurate guesses. Moreover, formalization of the estimation process will assist in resolving disagreements between observers in their estimates of left ventricular ejection fraction. The regional wall motion scores that are required by all the methods described here have independent clinical value, which is lost when a gross educated guess alone is used to estimate the ejection fraction.

The impact of differences in the end-diastolic volumes of the quadrants has been ignored in the models described here. Our results suggest that this is a valid assumption in the vast majority of cases. Even ventricles with marked dyskinesis usually have a smooth end-diastolic contour and the assumption of approximately equal quadrant end-diastolic volumes is not unreasonable. It would not be difficult to modify the models to take the drastic exceptions into account, although this would complicate the use of the method somewhat.

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Measurement of Intracardiac Dimensions and Structures in Normal Young Adult Subjects by Transesophageal Echocardiography

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Transesophageal echocardiography (TEE) has proven to be an excellent diagnostic means of diagnosing different cardiac diseases. To distinguish between normal and pathologic findings, standardized measurements of well-defined cross-sectional planes are necessary. Therefore, the 2-dimensional echocardiographic data of 25 healthy volunteers were obtained. In 13 men and 12 women, aged 19 to 30 years, recordings of the left ventricular short-axis view, the 2- or 4-chamber view with the left and right atria, the long axes of the left and right ventricles, the mitral and tricuspid valve ring and the atrial septum were analyzed. Furthermore, the aortic valve plane and the ascending and descending aorta were also measured. All data are given as mean values $\pm$ 2 times the standard deviation. End-diastolic and end-systolic left ventricular anterior-to-posterior diameter of the left ventricular short axis was 2.5 ± 0.3 cm/m² and 1.7 ± 0.3 cm/m², with the fractional shortening ranging from 27 to 42%. The end-systolic lateral diameter was 2.4 ± 0.5 cm/m² for the left atrium and 2.4 ± 0.4 cm/m² for the right atrium, and the end-systolic anterior-to-posterior diameter was 1.5 ± 0.6 cm/m² for the left atrium and 2.1 ± 0.6 cm/m² for the right atrium. End-diastolic diameters of 3.4 ± 0.6 cm/m² and 2.8 ± 0.4 cm/m² were obtained for the long axis of the left ventricle and for the right ventricle. Measurements ranged from 1.5 to 2.2 cm/m² for the end-diastolic diameter of the mitral ring and from 1.3 to 2.0 cm/m² for the tricuspid ring. The area of the aortic valve plane was 4.0 ± 1.2 cm²/m² and those of the ascending and the descending aorta were 3.6 ± 1.0 cm²/m² and 1.9 ± 0.8 cm²/m². The values of the left ventricular axis, the pulmonary artery stem and right pulmonary artery in TEE corresponded very closely to those gained from transthoracic echocardiography. The normal values obtained in healthy young subjects should be taken into account in the diagnostic decision making in heart patients.

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Transesophageal echocardiography (TEE) has proved to be of diagnostic value whenever the value of transthoracic echocardiography is limited by anatomical conditions (chest deformity, emphysema, obesity, postoperative status) or the use of transthoracic echocardiography causes logistic problems (intraoperative echocardiographic examination). Its application is particularly indicated when pathologic changes of the atria, the atrial septum, the atrioventricular valves or the aortic valve are assumed despite negative results on the transthoracic approach.¹⁻³ This may be the case in patients with clinically suspected endocarditis or tumor or thrombus of the heart.⁴⁻⁷ Furthermore, with TEE the diagnosis of a dissecting aneurysm of the thoracic aorta (ascending and descending parts excluding the upper part of the aortic arch) can be made with high sensitivity and specificity, identifying the true and false lumen and visualizing of the "entry tear."⁸⁻¹² Transesophageal color-coded Doppler can now also be used, further facilitating the diagnostic procedure.¹³ Intraoperative TEE allows continuous monitoring of left ventricular function; in combination with contrast agents, it is possible to assess valve function intraoperatively after surgical valve reconstruction.¹⁴⁻¹⁸

To help physicians to distinguish normal and pathologic findings in patients and enable TEE to become a routinely applied diagnostic method, it is necessary to standardize values of the "normal" heart structures and dimensions, as seen on transesophageal echocardiogram.

METHODS

The results in this study come from 25 of 28 healthy volunteers, 13 men and 12 women ranging in age from 19 to 30 years (mean age 23). The body surface area ranged from 1.53 to 2.22 m² with a mean of 1.85. In 3 persons, the examination had to be stopped early because of marked discomfort. The persons' histories were carefully evaluated for signs of esophageal disease. A fasting period of ≥ 6 hours was required before beginning the transesophageal examination. The pharynx was locally anesthetized with lidocaine; no further premedication was given. Antiarrhythmic drugs were available for injection if necessary. The esophagus transducer was introduced with the patient in the left lateral supine position.

We used a flexible conventional 12-mm endoscope in which the fiberoptic is replaced by a 3.5-MHz transducer fitted into the distal end of the scope. The so called echoscope was connected to an electronic phased array

sector scanner (Diasonics V 6400 R) for M-mode and 2-dimensional echocardiography. It is necessary to rotate and move the transducer up and down to visualize the different heart structures, as described previously, because only horizontal cross-sectional planes of the heart can be obtained with the available transducer.¹⁹ In addition to the use of time gain compensation, slope and reject, the echocardiogram quality was increased by inflecting the transducer toward the heart in order to keep esophageal secretion from being interposed.

The measurements were made on the echocardiograms giving the most detailed information with the ultrasound penetration usually being 10 to 15 cm. All echocardiograms were stored on videotape (VHS system) for subsequent electrocardiographically triggered, frame-by-frame analysis.

Complications during or after the procedures were not observed. In some persons, there was a mild sinus tachycardia at the beginning of the examination while the echoscope was being introduced into the esophagus. Some others complained of mild retching during the procedure.

Statistics: The results reported here are mean values with double standard deviation and are based on the analysis of 3 heart cycles. Furthermore, tolerance limits are listed using different factors because of the different number in each subgroup.

RESULTS

Left ventricular short-axis view: The examination started with the left ventricular short-axis view, which in most cases is an almost transgastral cross-section about 30 to 35 cm from the person's teeth. The anterior-to-posterior (sagittal) and left-to-right (frontal) di-

ameters of the left ventricular cavity were measured at the level of the papillary muscles just below the mitral valve leaflets (Figure 1). The fractional shortening was determined for the frontal and sagittal axes (Table I).

Left and right 2-chamber view: By withdrawing the echoscope several centimeters to a more cranial position, the transducer can be placed just behind the mid-level of the left atrium in a manner that the left atrium, the mitral valve and the left ventricle, or, by slight clockwise rotation of the scope, the right atrium, the tricuspid valve and the right ventricle can be visualized (Figure 2). The left atrial, left ventricular and mitral ring diameters were measured in a cross-section, with the maximal opening of the mitral valve leaflets in diastole and in systole (Figures 1B and 2A, Table I). The diameters of the right atrium, the tricuspid valve ring and the right ventricle were measured in the same way (Figures 2B and 3, Table I).

For the left atrium, we measured 2 diameters in diastole and systole, the sagittal axis from the coaptation of the closed mitral leaflets in a 90° angle to the mitral valve area up to the posterior left atrial wall and the frontal axis at half of this length from the lateral to the medial wall (atrial septum) parallel to the mitral valve area (Figure 1B, Table I).

The long axis of the left ventricle was taken from the coaptation of the closed mitral leaflets to the endocardium of the "apex." The apical left ventricular region on TEE corresponds to the anterior medial part of the left ventricular myocardium. The short axis was measured at half of this length in a 90° angle to the long axis (Figure 2A, Table I).

The mitral ring diameter was analyzed in end-diastole (Figures 1B and 2A, Table I); in most cases, the

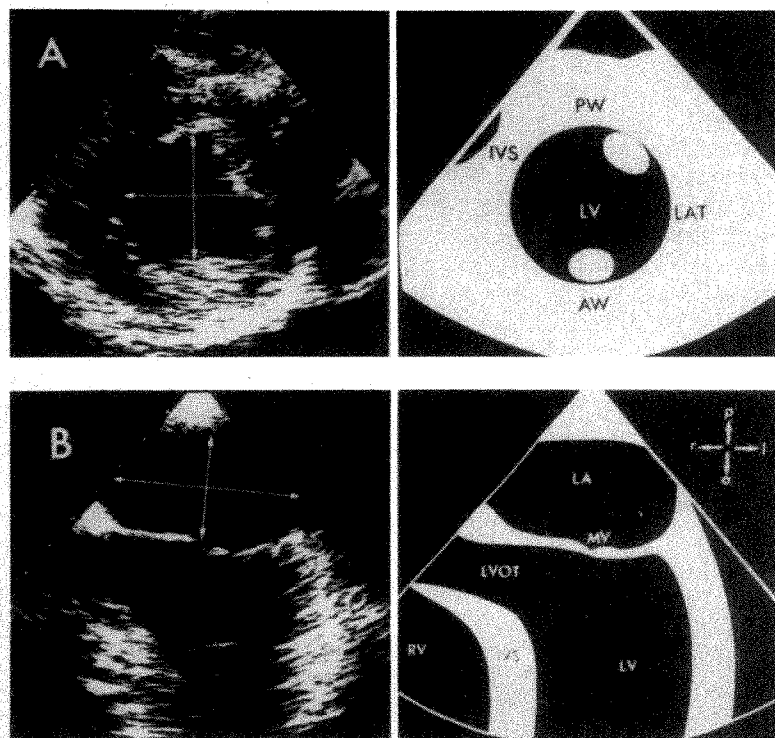


FIGURE 1. A, diameters (anterior-posterior and lateral) of left ventricular short axis. B, anterior-posterior and lateral diameters of left atrium. AW = anterior wall; IVS = interventricular septum; LA = left atrium; LAT = lateral wall; LV = left ventricle; LVOT = left ventricular outflow tract; MV = mitral valve; PW = posterior wall; RV = right ventricle; TV = tricuspid valve.

mitral ring could not be visualized clearly in systole. In ventricular systole, the left and right atria look almost circular or elliptical (Figure 3A). In diastole, the right atrium often resembles a triangular or trapezoidal figure while the left atrium keeps its shape in most cases. As a result, the lateral part of the tricuspid ring moves posteriorly while the septal part moves only slightly (Figure 3B).

To guarantee a reproducible measurement independent of the shape of the right atrium in any individual, we defined 1 axis from the middle of the tricuspid valve area to the posterior right atrial wall parallel to the atrial septum. The lateral axis was determined at half of this length parallel to the tricuspid valve plane; in most cases there is consequently not a 90° angle between both axes, in contrast to the left atrial measurements.

FIGURE 2. Long and minor axes of left (A) and right ventricles (B). RA = right atrium. Other abbreviations as in Figure 1.

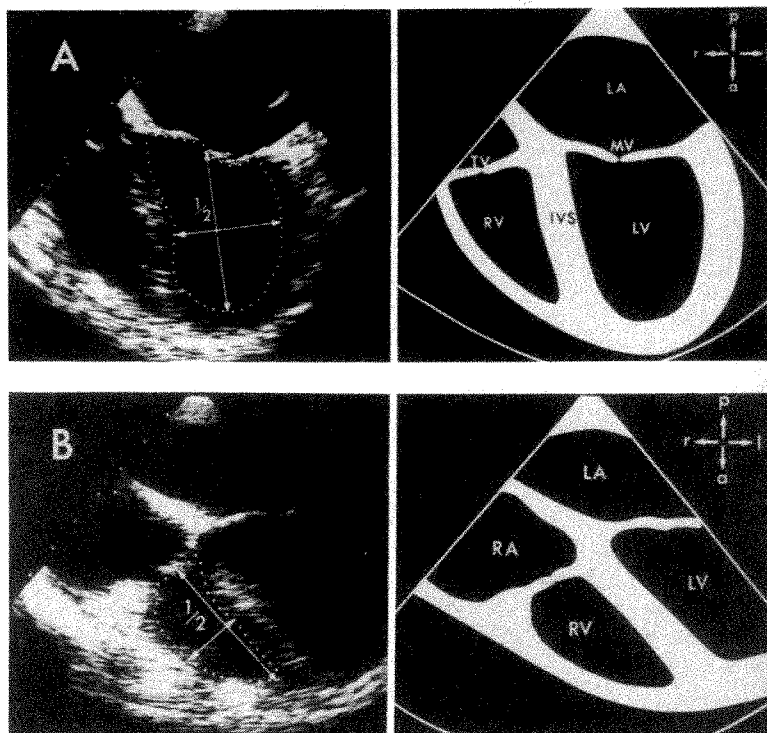


FIGURE 3. End-systolic and end-diastolic views with anterior-posterior and lateral diameter of right atrium. Abbreviations as in Figure 1.

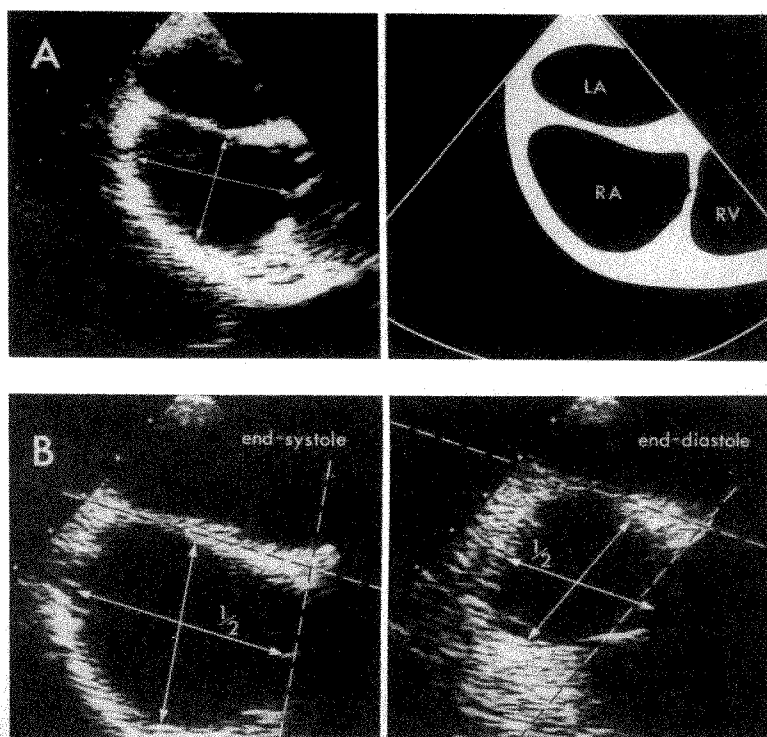


TABLE I Measurements in Normal Young Adult Subjects by Transesophageal Echocardiography

Patient	Age (yrs)	Body Surface (m ²)	Left Ventricular Short Axis (cm/m ²)				Fractional Shortening		Left Ventricular Long Axis (cm/m ²)				Left Atrium (cm/m ²)				Right Ventricular Long Axis (cm/m ²)			
			D	D	S	S	D(%)	D(%)	D	D	S	S	D	D	S	S	D	D	S	S
			↔	↑	↔	↑	↔	↑	↔	↑	↔	↑	↑	↔	↑	↔	↑	↔	↑	↔
1	24	2.09	2.5	2.6	1.5	1.7	40	34	—	—	—	—	1.0	2.0	1.7	2.5	—	—	—	—
2	29	2.12	—	—	—	—	—	—	2.6	3.6	1.8	2.7	0.8	1.7	1.1	2.4	—	—	—	—
3	24	1.65	2.5	2.6	1.6	1.6	37	37	—	—	—	—	0.8	1.7	1.4	2.5	—	—	—	—
4	23	1.91	—	—	—	—	—	—	2.8	3.9	2.0	3.3	1.4	1.4	1.9	2.1	2.5	1.5	2.0	1.0
5	26	2.22	—	—	—	—	—	—	2.4	3.1	1.6	2.4	—	—	—	—	2.7	1.7	2.3	1.2
6	22	1.79	2.4	2.4	1.6	1.6	35	34	2.5	3.1	1.6	2.4	0.7	1.7	1.4	2.3	2.6	1.3	2.2	1.0
7	30	2.08	3.0	2.7	1.8	1.7	42	36	2.4	3.4	1.6	2.7	1.3	1.8	1.9	2.6	2.7	1.6	2.2	1.2
8	22	2.05	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
9	22	1.67	—	—	—	—	—	—	2.8	3.5	2.2	3.0	0.4	1.1	1.1	2.2	2.8	1.8	2.5	1.2
10	22	1.89	—	—	—	—	—	—	2.7	3.1	1.8	2.7	—	—	—	—	2.5	1.3	2.0	1.0
11	19	1.67	2.5	2.5	1.5	1.5	41	38	2.3	3.0	1.7	2.4	0.8	1.7	1.4	2.3	2.7	1.2	2.4	0.8
12	27	1.55	2.9	2.9	1.8	1.9	38	34	2.9	3.4	2.0	2.5	0.4	1.5	1.4	2.8	—	—	—	—
13	24	1.87	2.5	2.6	1.7	1.9	31	27	—	—	—	—	—	—	—	—	2.8	1.6	2.3	0.9
14	23	2.00	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3.1	1.6	2.6	1.1
15	26	2.06	2.8	2.6	1.8	1.9	35	27	—	—	—	—	0.6	1.3	1.2	2.1	2.8	1.5	2.2	0.9
16	22	1.84	2.7	2.6	1.7	1.7	35	36	—	—	—	—	—	—	—	—	—	—	—	—
17	22	1.83	2.4	2.4	1.6	1.6	34	31	—	—	—	—	—	—	—	—	2.7	1.3	2.3	1.1
18	22	1.73	2.6	2.6	1.9	1.8	28	30	—	—	—	—	—	—	—	—	2.4	1.3	2.1	0.9
19	23	1.82	2.5	2.5	1.6	1.7	35	33	2.6	2.9	1.9	2.5	0.5	1.7	1.2	2.3	2.9	1.6	2.2	1.0
20	25	1.61	—	—	—	—	—	—	2.4	3.7	1.7	2.8	0.9	1.4	1.8	2.5	2.9	1.6	2.3	1.0
21	23	1.86	—	—	—	—	—	—	2.5	3.1	1.7	2.6	0.8	1.5	1.4	2.1	3.0	1.4	2.6	1.1
22	22	1.53	2.5	2.3	1.7	1.6	29	42	2.6	3.7	1.9	2.8	1.2	1.8	2.0	2.7	3.0	1.3	2.4	1.0
23	20	1.55	2.6	2.5	1.5	1.7	38	37	—	—	—	—	—	—	—	—	—	—	—	—
24	23	2.07	2.6	2.4	1.8	1.6	30	31	2.5	3.0	2.0	2.3	—	—	—	—	2.6	1.3	1.9	0.8
25	22	1.83	2.3	2.2	1.5	1.5	39	31	2.5	3.7	1.9	2.9	1.4	1.5	2.1	2.8	2.9	2.0	2.4	1.2
Mean			2.6	2.5	1.7	1.7	35	34	2.6	3.4	1.8	2.7	0.9	1.6	1.5	2.4	2.8	1.6	2.3	1.0
± 2 SD			0.4	0.3	0.3	0.3	8	8	0.4	0.6	0.4	0.5	0.7	0.4	0.6	0.5	0.4	0.3	0.4	0.2
Tolerance			2.1–	2.1–	1.3–	1.3–	25–	23–	2.1–	2.7–	1.3–	2.1–	0.1–	1.1–	0.9–	1.8–	2.3–	1.2	1.8	0.8–
			3.1	2.9	2.1	2.1	45	43	3.1	4.1	2.3	3.3	1.8	2.1	2.1	3.0	3.3	2.0	2.8	1.2

Mean values and double standard deviation ($x \pm 2$ SD) and tolerance limits for all cardiac and extracardiac structures and dimensions measured by transesophageal echocardiography.

D = end-diastole; S = end-systole; ↔, ↗ = lateral axes; ↑, ↘ = sagittal axes; ↔ = lateral axes; ● = cross-sectional area.

The atrial septum can be visualized in its full length in this cross-sectional plane and was analyzed in end-systole and end-diastole (Figure 3, Table I).

The axes of the right ventricular cavity were evaluated in the same way as those of the left ventricle (Figure 2B, Table I). The tricuspid ring diameter was assessed in diastole and systole (Figure 2B and 3A, Table I).

Aortic and pulmonary artery view: When the transducer is in a more proximal position in the esophagus, the aortic valve leaflets can be seen. In end-diastole, the commissures of the leaflets can be easily identified. The aortic ring almost forms a circle. The anterior-posterior

and frontal diameters were determined, as was the area of the aortic ring (Table I).

About 1 to 2 cm higher, passing the aortic sinus with its bulging aortic wall next to the aortic leaflets, the same measurements were performed for the ascending aorta (Figure 4A, Table I). By slightly inflecting the echoscope, the pulmonary artery stem and the right pulmonary artery passing behind the ascending aorta are visible. We measured the diastolic diameter of the pulmonary artery stem and the right pulmonary artery as indicated in Figure 4B and Table I.

By rotating the scope about 180° clockwise at the

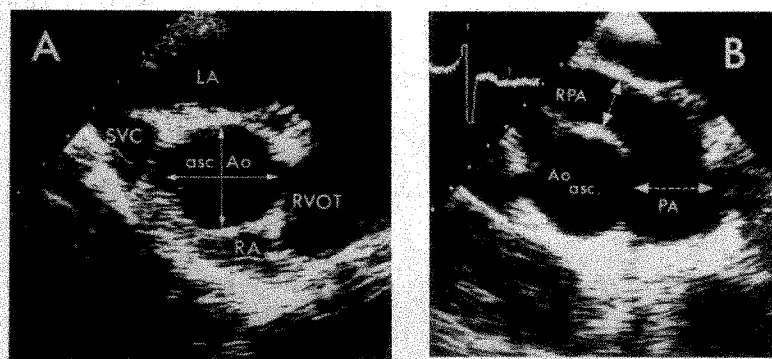


FIGURE 4. A, anterior-posterior and lateral axes of ascending aorta. B, point at which we measured right pulmonary artery is indicated. asc Ao = ascending aorta; LA = left atrium; PA = pulmonary artery stem; RPA = right pulmonary artery; RVOT = right ventricular outflow tract; SVC = superior vena cava.

TABLE I Continued

TABLE 1 Continued																					
Right Atrium (cm/m ²)				Aortic Valve cm/m ²			Asc Aorta cm ² /m ²			Desc Aorta cm ² /m ²			Tricuspid Ring (cm/m ²)			Mitral Ring cm/m ²		Atrial Septum (cm)		Right Main Pulmonary Artery (cm)	
D	D	S	S	D	D		D	D		D	D		D	S		D	S				
/	\	/	\	†	↔	●	†	↔	●	†	↔	●				○			○	○	
—	—	—	—	1.6	1.8	4.5	1.3	1.8	3.7	0.8	1.3	1.8	—	—	1.8	—	—	—	—		
—	—	—	—	1.3	1.7	3.3	1.3	1.7	3.7	0.8	1.1	1.6	—	—	1.8	—	—	—	—		
—	—	—	—	1.7	2.0	4.8	1.6	1.9	4.1	—	—	—	—	—	2.2	—	—	—	—		
1.8	2.4	2.4	2.6	1.3	1.7	3.4	—	—	—	1.0	1.3	2.1	1.8	1.4	1.9	1.6	2.1	1.2	1.8		
—	—	—	—	1.4	1.7	4.1	1.5	1.9	5.1	1.0	1.2	2.3	1.7	1.4	1.5	—	—	—	—		
1.9	1.8	2.5	1.9	1.3	1.7	2.8	1.5	1.7	3.5	0.9	1.4	1.8	1.6	1.0	1.5	1.6	2.1	1.2	2.1		
2.2	2.2	2.4	2.4	1.5	1.9	4.5	—	—	—	0.9	1.4	2.1	1.8	1.3	1.8	1.6	2.1	1.4	2.1		
—	—	—	—	1.4	1.8	4.0	1.3	1.7	3.6	0.9	1.2	1.7	—	—	1.8	—	—	—	—		
1.8	1.9	2.5	1.8	1.5	1.7	3.4	—	—	—	—	—	—	1.7	1.2	1.7	1.4	1.8	1.2	1.8		
1.8	1.8	2.0	2.0	—	—	—	1.3	1.8	3.8	—	—	—	1.5	1.5	1.5	1.6	2.2	1.1	1.6		
1.9	1.7	2.4	1.8	1.5	2.0	3.9	1.6	1.8	4.0	0.8	1.3	1.5	1.3	1.2	1.5	1.7	2.2	1.4	—		
—	—	—	—	1.3	1.9	3.3	1.3	1.8	3.1	1.0	1.3	1.6	—	—	1.9	—	—	—	—		
—	—	—	—	1.5	1.7	4.6	—	—	—	1.0	1.4	2.2	—	—	—	—	—	—	—		
1.9	2.4	2.8	2.3	1.3	1.8	3.5	1.3	1.6	3.3	0.9	1.5	2.2	1.7	1.5	1.9	1.6	2.1	1.0	2.0		
—	—	—	—	1.5	1.8	4.4	1.2	1.5	3.1	0.9	1.3	1.9	2.0	1.5	1.9	—	—	—	—		
1.7	2.2	2.3	2.1	1.4	2.0	4.1	—	—	—	1.0	1.5	2.6	—	—	—	1.6	1.7	1.1	2.1		
1.7	2.0	2.3	2.2	1.6	2.1	4.8	—	—	—	0.9	1.4	1.4	1.7	1.4	—	1.4	1.7	1.2	2.2		
1.7	1.9	2.3	2.0	1.4	1.9	3.7	1.4	1.7	3.7	0.8	1.4	1.7	1.5	1.3	—	1.6	2.0	1.1	2.3		
1.9	2.4	2.7	2.7	1.5	2.1	4.7	1.3	1.6	3.1	0.9	1.2	1.6	1.8	1.4	1.7	1.2	1.8	1.2	2.0		
1.8	2.1	2.7	1.9	1.5	2.2	5.1	1.5	1.9	3.7	0.9	1.4	2.3	1.7	1.5	2.0	1.9	2.6	1.0	2.0		
1.4	1.7	2.2	1.9	—	—	—	1.3	1.6	3.3	0.8	1.2	1.3	1.6	1.2	1.7	1.5	2.0	1.3	—		
2.2	1.9	3.0	2.0	1.6	2.1	4.8	1.7	1.9	4.2	0.8	1.3	1.8	1.5	1.4	2.1	1.9	2.7	1.0	—		
—	—	—	—	1.4	1.9	3.4	1.5	1.7	3.3	0.9	1.6	1.9	—	—	—	—	—	—	—		
1.9	2.4	2.2	2.4	—	—	—	—	—	—	1.1	1.5	2.7	1.8	1.4	—	1.4	1.7	—	—		
1.7	2.1	2.3	2.0	1.7	1.9	3.6	1.4	1.6	3.4	0.9	1.5	2.0	1.8	1.3	2.0	1.6	2.5	1.3	—		
1.8	2.1	2.4	2.1	1.5	1.9	4.0	1.4	1.7	3.6	0.9	1.3	1.9	1.7	1.4	1.8	1.6	2.1	1.2	2.0		
0.4	0.5	0.4	0.6	0.3	0.3	1.2	0.3	0.3	1.0	0.2	0.3	0.8	0.3	0.3	0.4	0.4	0.7	0.2	0.4		
1.3	1.6	1.9	1.5	1.2	1.6	2.8	1.0	1.4	2.4	0.7	1.0	1.1	1.3	1.0	1.3	1.1	1.2	0.9	1.5		
2.3	2.6	2.9	2.7	1.8	2.2	5.2	1.8	2.1	4.8	1.1	1.6	2.7	2.1	1.8	2.3	2.1	3.0	1.3	2.5		

level of the aortic valve, the cross-sectional plane of the descending aorta can be visualized, showing its more ellipsoid configuration (larger diameter in the frontal axis) on TEE. Both axes (frontal and sagittal) and the cross-sectional area were measured (Table I). The descending aorta can be scanned tomographically over a length of about 25 cm intrathoracically. We only made measurements of the clearly defined cross-sectional plane at the level of the aortic valve.

DISCUSSION

There has been increasing interest in TEE since it was first used clinically.¹ The diagnostic advantage offered by TEE, compared with conventional TTE in detecting most of the cardiac structures is well documented. A recent review by Shively and Schiller²⁰ summarizes the wide variety of applications and the clinical value of the method. The increasing clinical value and general availability of the method are making it more and more necessary to have more standard cross-sectional planes, well-defined measurements of the intracardiac dimensions and structures and extracardiac vessels. For this purpose, "normal" values must be established, while being aware of the fact that "normal" values may change with age. The age range (19 to 30 years) of this mixed age group indeed limits the applica-

bility of the data, which should be considered carefully when performing examinations in elderly patients. Because of the semiinvasive character and the discomfort of the method, the number and age of volunteers on whom a transesophageal study can be performed is limited.

An optimal view of all the heart structures of interest cannot be obtained in every patient. The aortic valve can be sufficiently visualized in nearly every case, whereas an exact measurement in the long axis view may be difficult or impossible in about a third of the cases. This is due to the variation in the anatomical relation between the esophagus and the heart or the aorta. This difficulty can be overcome to some extent by inflecting or rotating the transducer. Because the ultrasonic beam passes the left and right ventricle in an oblique way in the long-axis view, the identification of the apical endocardium may be difficult. If the use of the newer 5.0-MHz transducer systems will give more precise definition of the anatomy and whether the measurements will be different is unclear. Measurement of the left and right atrium may prove problematic when they are dilated. It may then be difficult to visualize the posterior and lateral borders. Thus, only a qualitative description of atrial size, without an exact measurement, is then possible. This is independent of the possi-

bility of detecting and giving a qualitative description of pathologic changes of the heart in TEE.

The values obtained for the diameter of the left ventricular short axis in diastole and systole, both taken at the level of the papillary muscles, correspond quite favorably with those obtained in the 2- and 4-chamber views (Table I). Consequently, these parameters of the left ventricle can be reliably obtained in 2 different cross-sectional planes, whichever has the best echocardiogram image quality.

Normal values for 2-dimensional TTE have been published by Erbel et al.²¹ and by Schnittger et al.²² It is of interest that their data for left ventricular end-diastolic (2.2 to 3.0 cm/m² and 2.2 to 3.1 cm/m²) and end-systolic diameter (1.4 to 2.0 cm/m² and 1.4 to 2.2 cm/m²) in the left ventricular short-axis view and the range of the fractional shortening (27 to 44% and 25 to 43%) correspond well with our TEE results (Table I). The results for the diameter of the aortic valve are also similar (1.0 to 1.7 cm/m² and 1.4 to 2.0 cm/m²). The diameters of the pulmonary artery stem (1.8 ± 0.6 cm) and the right pulmonary artery (1.2 ± 0.4 cm) have also been analyzed in the high parasternal short axis using TTE by Triulzi et al.²³ Their values corresponded to those we obtained with TEE (Table I). Thus, the results of the 2 different echocardiographic approaches (TTE and TEE) may be comparable in at least 2 cross-sectional planes.

With the transesophageal echocardiographic system now available, it is not possible to determine the end-systolic and end-diastolic left ventricular volumes and ejection fraction because of the difficulties mentioned previously. This situation might change if rotating transducer systems were available for different planes. This would make the relation of the esophagus to the heart more "flexible" and make it possible to measure a true long axis.

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Pharmacologic Management of Ventricular Arrhythmias After the Cardiac Arrhythmia Suppression Trial

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Sudden cardiac death is the most common cause of mortality in the adult population, accounting for over a half a million deaths in the United States each year.¹ Over 80% of these deaths are due to a ventricular tachyarrhythmia (VT), often preceded by ventricular ectopic activity (VEA) that degenerates into ventricular fibrillation without clinical evidence of ischemia.² The patient with VEA presents a major problem for clinical management. Clinical decision, which was always fraught with controversy, became even more problematic in 1989 with the release of the interim Cardiac Arrhythmia Suppression Trial (CAST) results.³ CAST has dictated a critical reexamination of the prognostic importance of VEA in the setting of coronary heart disease, appropriate methods of detection and classification and indications for drug therapy.

Relation of ventricular arrhythmias and left ventricular dysfunction to mortality after myocardial infarction: The relation between VEA, left ventricular (LV) dysfunction and mortality in coronary heart disease has remained controversial despite several large-scale clinical studies. Ventricular arrhythmias were somewhat more frequent and complex when LV scarring was present or the LV ejection fraction (EF) was decreased.⁴⁻⁷ The independence of VEA and LV dysfunction as predictors for cardiac mortality was suggested by 2 large studies that used crude measures of LV dysfunction and brief (1 to 6 hours) electrocardiographic recordings.^{8,9} Schultz et al⁶ first used LVEF to evaluate the relations among LV dysfunction, ventricular arrhythmias and sudden cardiac death in 81 patients recovering from myocardial infarction. However, only 8 deaths occurred in this study group of 26 patients who had both LVEF <0.40 and complex ventricular arrhythmias, making it impossible to separate the potential independent risk of LVEF and VEA.

Four large postmyocardial infarction studies used 24-hour continuous electrocardiographic (Holter) recordings to assess ventricular arrhythmia frequency and radionuclide or angiographic methods to measure

LVEF (Table I).^{5,10,11,12} There was no statistical interaction between VEA and LVEF with respect to their mortality effects, i.e., the mortality effects were independent. LVEF predicted early deaths (<6 months) better while the VEA predicted late deaths (>6 months) better. The information base that indicates an association between VEA and mortality after statistically controlling for LVEF has been criticized.¹³ The main 2 criticisms were a lack of a monotonic increase in risk as VEA frequency increased in the Multicenter Post Infarction Program and the lack of a statistically significant association between ventricular arrhythmia and mortality in each subgroup of the Multicenter Investigation of the Limitation of Infarct Size cross-classified by LVEF and VEA frequency. The requirement for a progressive increase in risk, with no deviations from trend, is an excessively stringent criterion.¹⁴ So long as the overall trend is in the hypothesized direction, a few categories that do not follow the trend, especially if their sample sizes are small, do not indicate that the overall trend is not statistically significant. There are reversals in the mortality trends for LVEF within 6 categories of VEA frequency; such exceptions to perfectly progressive trends, due to sampling variation, have never been cited as casting doubt on the prognostic importance of LVEF. The lack of statistical significance for the association between VEA and mortality in each of the 4 Multicenter Investigation of the Limitation of Infarct Size subgroups also is an excessively stringent criterion. It would be unrealistic to expect to have the power to have a statistically significant difference in all subgroups of a study that only had a total of 29 mortality events. The appropriate statistical test for significance is across all 4 subgroups together, controlling for LVEF.

Thus, VEA is an independent predictor of sudden cardiac death after myocardial infarction and, when present in such patients, presents the physician with a challenge in determining clinical management. Before reviewing the rationale for and the attempts to test the hypothesis that VEA suppression prevents sudden death, we will review a classification system for VEA and the electrocardiographic models used in clinical applications.

The prognostic classification system of ventricular arrhythmias: We have previously described a prognostic classification of ventricular arrhythmias based principally on the arrhythmia's potential for causing sudden cardiac death.^{15,16} This classification system (Table II) was used to clarify indications for antiarrhythmic drug therapy, guide the evaluation of therapy and predict

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TABLE I Relation Between Ventricular Arrhythmias, Left Ventricular Dysfunction and Mortality After Myocardial Infarction

Study	Total No. of Patients	LVEF <40%					LVEF ≥40%				
		VPC <10/hr		VPC ≥10/hr		Relative Risk	VPC <10/hr		VPC ≥10/hr		Relative Risk
		n	Mortality Rate (%)	n	Mortality Rate (%)		n	Mortality Rate (%)	n	Mortality Rate (%)	
MPIP	766	184	17.3	72	32.2	1.87	432	6.3	78	11.7	1.84
MILIS	533	141	19.1	40	40.0	2.09	314	5.1	38	18.4	3.61
MDPIT	955	203	15.2	75	30.2	1.99	589	7.0	88	12.6	1.81
UCSD SCOR*	749	84	17.9	101	26.7	1.50	357	5.0	207	14.5	2.87

Values for MPIP and MDPIT are Kaplan-Meier estimates of mortality rates at 24 months of follow-up; values for MILIS are crude mortality rates with average follow-up of 18 months.

* UCSD SCOR arrhythmia data are partitioned by Lown grade <2 and ≥2, thus, many patients with low frequency and no repetitive ventricular arrhythmias are in the ≥2 group. Mortality values are crude rates at end of 12 months of follow-up.

LVEF = left ventricular ejection fraction; MDPIT = multicenter diltiazem postinfarction trial; MILIS = Multicenter Investigation of the Limitation of Infarct Size; MPIP = Multicenter Postinfarction Program; UCSD SCOR = University of California San Diego Special Center of Research in Ischemia Heart Disease; VPC = ventricular premature complexes.

antiarrhythmic drug efficacy and cardiac adverse effect rates. The principal features used to classify arrhythmias are symptoms and the degree of underlying structural heart disease.

Ventricular arrhythmias are termed "benign" when they produce no hemodynamically important symptoms and there is no apparent structural cardiac disease. Such patients have minimal to no increased risk of sudden cardiac death.¹⁷ Antiarrhythmic drug therapy is indicated only to eliminate debilitating symptoms, despite reassurance. The benign class accounts for approximately 30% of patients with ventricular arrhythmias. Approximately 65% of patients with ventricular arrhythmias can be classified into the "potentially malignant class," which can also be termed "prognostically significant." Such patients have underlying structural cardiac disease often associated with LV dysfunction. Hemodynamically important cardiac symptoms are not present. This class is quite heterogeneous and the potential increase in sudden cardiac death risk ranges from modest to high. At one end of this spectrum are individuals who have minimal LV dysfunction with simple infrequent ventricular premature complexes (VPCs). These patients will have only a modest increase in sudden cardiac death risk. At higher risk are patients with clinical heart failure, LVEF <0.30 or possibly a positive signal-averaged electrocardiogram. Symptomatic relief is the only indication for treatment of potentially malignant arrhythmias. Only about 5% of ventricular arrhythmias are "malignant" or immediately life-threatening; this includes sustained VT or ventricular fibrillation. For inclusion in this category, the ventricular arrhythmia nearly always produces hemodynamically important signs or symptoms such as syncope, heart failure, myocardial ischemia or hypotension. These patients have the highest risk of sudden cardiac death and usually the most severe form of underlying cardiac disease. LVEF partitions these patients into high and very high-risk groups. Therapy is always indicated in these patients to control symptoms and to decrease the risk of sudden cardiac death.

Electrocardiographic methods to guide therapy: Before starting therapy for symptomatic benign ventricular arrhythmias, the physician usually should show an association between the arrhythmia and symptoms by electrocardiographic recordings.¹⁸ Exercise testing may

be required to bring out exercise-related unsustained VT. Electrophysiologic testing is usually not indicated for patients with benign arrhythmias. Patients with potentially malignant ventricular arrhythmias are managed similarly to benign arrhythmias. Electrophysiologic testing has been advocated by some to decide whether treatment should be given to patients with low LVEF and unsustained VT. If monomorphic sustained VT is induced, therapy is given under electrophysiologic guidance; if VT is not induced, no therapy is given. The data to support this approach have been contradictory,¹⁹ and this approach is still not an established practice. Clinical trials are planned to evaluate this approach. For patients with malignant ventricular arrhythmias, current practice favors the use of electrophysiologic-guided therapy over the noninvasive approach.²⁰ The electrophysiologic study versus electrocardiographic monitoring trial²¹ should provide controlled data comparing these 2 methods. Many clinicians use both modalities.

Signal-averaged electrocardiography is a diagnostic test to detect the cardiac "substrate" that supports sustained ventricular arrhythmias. The presence of delayed, low-amplitude activation in the terminal portion of the amplified QRS signal, the late potential, seems to be a moderately sensitive and a very specific indicator for inducible VT during electrophysiologic study.²² Preliminary data suggest that the signal-averaged electrocardiogram is more predictive than Holter-detected arrhythmic events.²³ The combination of an abnormal signal-averaged electrocardiogram, abnormal LVEF and the presence of "high grade" VEA on Holter recordings identified a small subset at very high risk for sustained VT or sudden cardiac death. The signal-averaged electrocardiogram is not useful for guiding drug therapy.

Rationale for clinical trials with antiarrhythmic drugs: Four large studies^{5,10,11,12} indicating an independent and reasonably strong association between VEA and subsequent mortality provided a strong scientific rationale for a large-scale clinical trial to determine if treatment of VEA after myocardial infarction will decrease sudden cardiac death.

May et al²⁴ and Furberg²⁵ reviewed clinical trials of antiarrhythmic drug therapy after myocardial infarction. Although these trials were flawed, no trend suggesting benefit was found in the long-term postmyocardial infarction antiarrhythmic drug trials (in fact, the

TABLE II Prognostic Class of Ventricular Arrhythmias

	Benign	Potentially Malignant		Malignant
		LVEF ≥ 0.30	LVEF < 0.30	
Sudden Cardiac Death Risk	Lowest	Moderate	High	Highest
Degree of Structural Heart Disease	None	Moderate	Moderately Severe	Severe
Hemodynamic Symptoms	Absent	Absent	Absent	Present
ECG Method of Evaluation	Noninvasive	Noninvasive	Noninvasive (or EPS)	EPS
Common Arrhythmic Type	VPCs	VPCs and USVT	VPCs and USVT	Sustained VT/VF

ECG = electrocardiographic; EPS = electrophysiologic testing; IA = antiarrhythmic drug with class IA action; IC = antiarrhythmic drug with class IC action; LVEF = left ventricular ejection fraction; VPCs = ventricular premature complexes; USVT = unsustained ventricular tachycardia; VF = ventricular fibrillation.

trend was toward the harmful boundary). It is interesting that the 2 studies did show encouraging results in enrolled patients who had ventricular arrhythmias and attempted to suppress ventricular arrhythmias by dosing with the active treatment.^{26,27}

The National Heart, Lung, and Blood Institute recognized that these previous clinical trials did not establish the feasibility of a full-scale trial to determine whether suppression of ventricular arrhythmias after myocardial infarction with antiarrhythmic drugs will improve survival or how to design a full-scale trial. Therefore, the Cardiac Arrhythmia Pilot Study was initiated to provide information on feasibility and design issues.²⁸ Between 1983 and 1985, 502 patients were enrolled 6 to 60 days after myocardial infarction. Patients were randomized to each of the following 5 treatment tracks: placebo and 4 active drugs; encainide; flecainide; imipramine; and moricizine. Encainide and flecainide achieved the goal for long-term efficacy and moricizine was close.²⁹ The adverse effect rates for active drugs were similar to placebo. The antiarrhythmic effects of these 3 drugs were sustained over the course of 1 year and the dropout rate was low. These results indicated that it was feasible to conduct a full-scale clinical trial to determine if suppression of ventricular arrhythmias with antiarrhythmic drug treatment after myocardial infarction would significantly decrease sudden cardiac death; the CAST was launched in June 1987.³ Until the results of that trial were available (projected then to be 1992), physicians were required to choose antiarrhythmic drug therapy based on their ability to estimate the relative benefits versus risks of such treatment with the understanding that there were no data to support or refute the use of antiarrhythmic drugs for patients with high-risk, potentially lethal VEA.

Antiarrhythmic drug comparisons: Relative efficacy and adverse effect profiles of oral antiarrhythmic drugs (available in the United States) have been frequently described in the context of the Vaughan-Williams clas-

sification. While drugs within the same subclass, e.g., IA, may have different profiles, the effects upon the electrocardiogram and the relative efficacy and some types of adverse effects tend to be related.³⁰ Nevertheless, each antiarrhythmic agent should be considered a unique entity. The subclassification of the traditional class I membrane-stabilizing antiarrhythmic drugs into A, B and C has become less useful in light of several new antiarrhythmic agents that do not fit into this system. The ability to predict drug potency in decreasing VPCs or unsustained VT is, however, a useful feature of this classification system. Table III lists antiarrhythmic drug potency on a 1+ to 4+ scale considering the percent of patients with benign or potentially malignant ventricular arrhythmias who meet efficacy reduction criteria using Holter evaluation. Antiarrhythmic drugs with subclass IC action clearly are associated with the greatest suppression of VPC and unsustained VT events compared to all other class I or II agents.

In patients with malignant ventricular arrhythmias evaluated by electrophysiologic testing, efficacy is best defined as the prevention of induction of uniform sustained VT on therapy compared to baseline. Table III defines also the relative potency of the oral antiarrhythmic drugs evaluated in this way using a 1+ to 4+ scale. There is a marked difference among the various antiarrhythmic drugs by subclasses in their ability to decrease VPCs and unsustained VT using Holter monitoring in patients with benign or potentially malignant ventricular arrhythmias. However, there is a relatively narrow range of effectiveness when using the electrophysiologic testing schema in patients with malignant ventricular arrhythmias.

Antiarrhythmic agents, like other drugs, may cause noncardiac adverse effects and organ toxicity. Table III lists the comparative likelihood of adverse effects by antiarrhythmic drug and ventricular arrhythmia classes. Patients with severe LV dysfunction and sustained ventricular arrhythmias have a higher risk of cardiac adverse effects (particularly proarrhythmia and congestive heart failure).³¹ Risk of noncardiac adverse effects and organ toxicity are more drug-specific and not predictable by ventricular arrhythmia class. Organ toxicity must be carefully considered by physicians in their risk versus benefit assessment. For example, quinidine and procainamide are the most frequently prescribed antiarrhythmic drugs in the United States, despite the fact that they have a high noncardiac adverse effect rate (25 to 35%) and also a high degree of organ toxicity. Procainamide, for example, has an approximate 1 in 200 to 1 in 2,000 chance of agranulocytosis with an associated 25% mortality rate, which is comparable to the rate of agranulocytosis from tocainide. Agents that can commonly cause organ toxicity should not be considered "first line" drugs when given to patients with benign or potentially malignant ventricular arrhythmias because the benefit of therapy in these patient groups is limited and the potential risk from organ toxicity is high.

The adverse cardiac effect now frequently called "proarrhythmia" became commonly recognized in the 1980s as a result of the clinical trials of drugs with IC antiarrhythmic action. Before that time, quinidine syn-

TABLE III Antiarrhythmic Drug Potency and Risk of Adverse Effects

AA Drug Class	Relative Efficacy		Risk of NCAE (%)	Risk of Organ Toxicity	Risk of Early-Occurring Serious Proarrhythmia		Risk of CHF	
							B/PM	M
	B/PM	M			B/PM	M	LVEF ≥ 0.30 NYHA I and II	LVEF 0.030 NYHA III and IV
I								
Moric	3+	2+	10	None-low	Low	Low	0	1+
IA								
Quin	3+	2+	25	Mod	Mod	Mod	0	0
Proc	2+	2+	25	High	Mod	Mod	0-1+	1+
Diso	2+	1+	35	None-low	Mod	Mod	2+	4+
IB								
Toc	2+	1+	40	High	Low	Low	0	0
Mex	2+	1+	40	Low	Low	Low	0	0
IC								
Enc	4+	2+	10	None-low	Low	High	0	1+
Flec	4+	2+	10	None-low	Low	High	1+	4+
Propa	3+	2+	20	Low	Low	High	1+	3+
II								
BB	2+	0- 1+	10	None-low	Low	Low	1+	3+
III								
Amio	NA	3+	High	Highest	NA	Low	0-1+	1+

AA = antiarrhythmic; Amio = amiodarone; B = benign ventricular arrhythmia class; BB = β blocker; CHF = congestive heart failure; Diso = disopyramide; Enc = encainide; Flec = flecainide; LVEF = left ventricular ejection fraction; M = malignant; Mex = mexiletine; Mod = moderate; NA = not applicable; Moric = moricizine; NCAE = noncardiac adverse effects; NYHA = New York Heart Association; PM = potentially malignant ventricular arrhythmia class; Proc = procainamide; Propa = propafenone; Quin = quinidine; Toc = tocainide.

cope had been documented as often due to torsades des pointes, though the prevalence was and still is unclear. Proarrhythmia has been defined as any new, more advanced form of arrhythmia, especially when producing hemodynamically important symptoms and occurring early (<30 days) after treatment initiation and not due to a new event, e.g., acute myocardial infarction, hypokalemia and so forth.³² A drug-associated increased frequency of VEA (proarrhythmia) must be differentiated from inefficacy coupled with spontaneous variability.³³ The distinction is important because proarrhythmia suggests that that antiarrhythmic drug should be avoided, whereas lack of efficacy may require an increase in drug dose. The potential for negative inotropic effects requires consideration of left ventricular function in terms of its systolic and diastolic components. The systolic function may be estimated by the LVEF and the diastolic function may be best reflected by the patient's New York Heart Association symptomatic class. Patients with a baseline LVEF ≥ 0.30 and with New York Heart Association class I and II (the most common group of patients) rarely have new onset or worsening of congestive heart failure from antiarrhythmic drugs.³⁴ The exception to this rule may be disopyramide, although it too is generally well tolerated in this population. Patients with LVEF at baseline <0.30 and/or New York Heart Association class III and IV are more sensitive to the negative inotropic effects of antiarrhythmic agents. Disopyramide, flecainide and probably β blockers need to be used with caution or avoided when this degree of LV dysfunction exists.

Clinical use of antiarrhythmic drugs before release of the interim Cardiac Arrhythmia Suppression Trial results: Surveys of cardiologists in the United States have identified that the degree of symptoms, complexity

of the ventricular arrhythmia present and the degree of underlying structural heart disease are the principal features that govern antiarrhythmic drug prescription.^{35,36} In a recent survey,³⁵ only 1% of cardiologists prescribed antiarrhythmic therapy for patients with no heart disease and asymptomatic VPCs, whereas about 50% prescribed such drugs to patients with prior myocardial infarction with asymptomatic ventricular ectopy, a group comparable to the CAST study population. All cardiologists who responded treated patients who had symptomatic, sustained VT.

Because of their high efficacy and low overall adverse effect profile, we have previously recommended first-line consideration for the class IC antiarrhythmic agents such as flecainide and encainide when therapy for benign or potentially malignant ventricular arrhythmias was warranted, such as the relief of clinically important symptoms. However, the release of the preliminary CAST results³ has had an impact on the risk/benefit for the use of encainide, flecainide and other antiarrhythmic drugs in patients with benign or potentially malignant ventricular arrhythmias.

The results of the Cardiac Arrhythmia Suppression Trial: The principal objective of CAST was to determine whether suppressing potentially malignant ventricular arrhythmias would decrease death from arrhythmia. The interim results³ showing that encainide and flecainide increased mortality compared to placebo disprove the hypothesis that suppression of potentially lethal VEA prevents arrhythmic disease, at least for these 2 drugs. It would have been useful to define such data for quinidine, procainamide, disopyramide, mexiletine and tocainide. These drugs were not selected for CAST or the Cardiac Arrhythmia Pilot Study because previous studies suggested that they were either not potent in

suppressing VEA and/or they had a higher adverse effect rate that would dictate an excessive sample size used for a large scale trial.

Overall, the mortality rate of patients entering open-label titration in CAST was about that anticipated from previous postinfarction populations. However, after randomization, the CAST placebo group had a low arrhythmic death rate (about half of that expected). This finding was primarily due to the selection of a low-risk population for sudden cardiac death identified by VEA suppression during drug titration. Prior trials that had found a decrease in sudden death in patients whose ventricular arrhythmias were suppressed with antiarrhythmic drugs compared to nonresponders may, in fact, have been on the basis of identifying patients with a subsequent reduced risk of death rather than the reduced death rate being due to the antiarrhythmic drug's suppression.³⁷

The fact that encainide or flecainide produced a worse outcome, opposite of predicted, in patients with potentially malignant ventricular arrhythmias, raises new concerns about the risk versus benefit of antiarrhythmic drug therapy. Results of CAST cannot be directly extrapolated to patients with symptomatic benign ventricular arrhythmias or those with supraventricular arrhythmias with normal hearts. Nevertheless, encainide and flecainide and other agents with class IC action should be used with a higher threshold in such patients until their safety has been shown. However, therapy with such drugs having class IC antiarrhythmic action is so useful in patients with these conditions (high efficacy with low noncardiac adverse effects and organ

toxicity) that their continued use for such patients is reasonable as long as one considers carefully the potential increase in mortality (albeit small) that might occur. One would generally avoid the use of drugs with class IC action in any patient who presents with a scarred ventricle or with reduced LVEF, because in these groups the cardiac adverse effects may be enhanced.

Mechanism of enhanced mortality in Cardiac Arrhythmic Suppression Trial: The mechanism of increased mortality in patients treated with encainide or flecainide in CAST is not known. The mortality in CAST can thus be considered a "late" proarrhythmic response to flecainide and encainide, and this event should be distinguished from the "early" proarrhythmic phenomena that are seen within the first 30 days after initiating antiarrhythmic agents. Early proarrhythmia with encainide or flecainide appears to occur in patients in whom VPC and unsustained VT episodes are not suppressed and can be related to excess dose rate of drug administration or the occurrence of electrocardiographic markers such as a prolonged QRS interval. Separating "early" from "late" proarrhythmia allows for comparisons of the types and rates of early proarrhythmic side effects from old versus new antiarrhythmic drugs since identification of "late" proarrhythmic effects requires controlled mortality trials such as CAST.

It is not clear how encainide or flecainide might exert their adverse effect on mortality. Some general possibilities are as follows: they make sustained reentrant ventricular arrhythmias more likely by increasing the

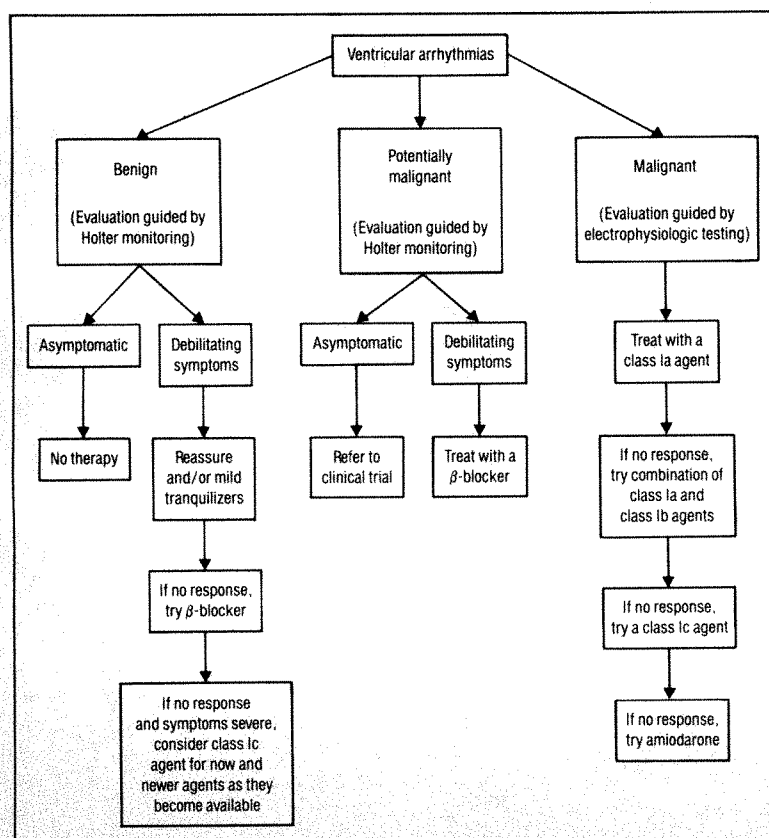


FIGURE 1. Algorithm for treatment of ventricular arrhythmias, 1990. Reproduced with permission from *Primary Cardiology* 1990;16:42.

relative infarct size; they depress left ventricular function; they increase ischemia; or they increase the likelihood of fatal ventricular arrhythmias during ischemia or periods of increased sympathetic nervous system activity. Our working hypothesis to explain the increased mortality in the encainide/flecainide treated groups in CAST is an adverse interaction between these drugs and episodes of myocardial ischemia that promote ventricular fibrillation. Some of the encainide/flecainide-associated deaths may be due to VT promoted by drug-induced conduction slowing. It seems unlikely that this mechanism accounts for many of the drug-associated deaths. Otherwise, there should have been a higher relative risk of nonfatal, sustained VT in the encainide/flecainide-treated groups. An interaction between drug treatment and ischemia or autonomic nervous activity is the most likely explanation.

Implications of the Cardiac Arrhythmias Suppression Trial for drug therapy: It is unknown whether other class I or all antiarrhythmic agents may act similarly to encainide and flecainide. CAST is continuing with moricizine suggesting that not all class I agents increase sudden death rate in patients with potentially malignant ventricular arrhythmias. Until CAST is concluded or other similar large-scale mortality trials are conducted, one should not assume that any class I antiarrhythmic drug (especially those that commonly cause early proarrhythmia) can be used safely for the treatment of potentially malignant arrhythmias with the hope that sudden cardiac death will be prevented. A recent meta analysis of 808 patients participating in 6 quinidine trials for control of atrial fibrillation showed a 3-fold increase in total mortality in those on quinidine (2.9%) versus placebo (0.8%).³⁸ There was an increased mortality rate observed in postmyocardial infarction patients treated with mexiletine compared to placebo and this agent has modest potency for suppressing VEA and a high frequency of noncardiac side effects.^{39,40} These facts suggest that drugs with class IA or IB action should not be assumed to be useful or safe in patients with postinfarction symptomatic ventricular arrhythmias.

Beta blockers, despite the fact that they have modest potency for suppressing VEA, nonetheless have minimal risks for organ toxicity, noncardiac adverse effects and cardiac adverse effects such as proarrhythmia, and have been shown to decrease mortality and sudden cardiac death risk after myocardial infarction.⁴¹ Thus, β blockers should be considered the "first-line" antiarrhythmic drug of choice in the treatment of patients with debilitating symptoms who have benign or potentially malignant ventricular arrhythmias.

For now, patients with underlying heart disease and asymptomatic ventricular arrhythmias should receive β blockers and not class I antiarrhythmic drugs to prevent sudden cardiac death. Such patients should be referred to trials that are designed to provide the data in this area. One needs to rethink the use of all antiarrhythmic drugs in light of the results of CAST since the potential for risk (i.e., increased mortality) is now apparent. It is hoped that these results will not impede new antiarrhythmic drug development, but it is expected that mor-

talidity data will be necessary if new antiarrhythmic drugs wish to have a claim for treatment of patients with asymptomatic or even symptomatic potentially malignant ventricular arrhythmias. CAST has been a valuable clinical trial in providing to physicians a hitherto unknown and surprising outcome that should markedly affect the practice of medicine and potentially save thousands of lives in the United States, which otherwise could be lost from the inappropriate use of antiarrhythmic drugs.

Summary and an algorithm for antiarrhythmic drug therapy for symptomatic ventricular arrhythmias: An algorithmic approach (Figure 1) to the use of antiarrhythmic drug therapy is principally based on a risk versus benefit assessment, which may be guided by classifying a ventricular arrhythmia as benign, potentially malignant or malignant. In patients with benign ventricular arrhythmias, no antiarrhythmic therapy is indicated unless debilitating lifestyle-limiting symptoms cannot be eliminated by reassurance or intermittent mild tranquilization. When antiarrhythmic drug therapy is indicated, a β blocker is the agent of choice because of lack of organ toxicity, low risk of noncardiac or cardiac adverse effects and evidence proving a decrease in sudden cardiac death in a postmyocardial infarction population.⁴¹ If β blockers fail, we would consider the use of antiarrhythmic agents with class IC action if the impact of debilitating symptoms are so important that the potential for increasing mortality is justified. We prefer antiarrhythmic agents with class IC action in this group of patients over agents with class IA and IB action in light of their relatively high degree of efficacy and low risk of noncardiac, cardiac and organ toxic adverse effects.

If new antiarrhythmic agents become available for the treatment of ventricular arrhythmias in the United States, the algorithm for selecting drugs for the treatment of serious symptomatic benign or potentially malignant ventricular arrhythmias will change. Agents that do not have the potential for increasing mortality, but maintain high efficacy with low potential for cardiac, noncardiac and organ toxic adverse effects may become preferable even to β blockers. For example, if moricizine should prove to decrease sudden cardiac death in the extension of CAST, it will become the "first-choice" agent for the prophylactic treatment of patients with ventricular arrhythmias. If moricizine is shown only to be safe in CAST, but does not decrease mortality, it still will be the first choice for the treatment of symptomatic, potentially malignant VEA after β blockers.

In patients with malignant ventricular arrhythmias, agents with class IA action appear to be the most appropriate drugs for initial therapy followed by combination of agents with IA and IB action and finally antiarrhythmic agents with class IC effects. Because of encainide and flecainide's higher rates of proarrhythmia and with flecainide's high rate of negative inotropic effect compared to agents with class IA and IB actions, we use them just before the most toxic antiarrhythmic drug in this sequence, amiodarone.

Patients with potentially malignant ventricular arrhythmias without symptoms should not be treated with antiarrhythmic drugs, and, if possible, such patients should be referred to clinical trials such as CAST to assess the potential for reducing sudden cardiac death. In patients whose symptoms require reduction because of lifestyle-limiting effects, β blockers should be initiated if not already used. Selection of other antiarrhythmic agents beyond β blockers at this time is unclear, pending the results of further clinical trials and the availability of new antiarrhythmic agents.

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Effects of Left Ventricular Hypertrophy on the Coronary Circulation

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When the heart is exposed to an excess pressure or volume overload, myocardial hypertrophy occurs as a compensatory process that results in normalization of wall stress. After normalization of the wall stress, the hypertrophy stabilizes and there is no subsequent change in ventricular volume or cardiac mass.¹ Left ventricular (LV) myocardial oxygen consumption and myocardial perfusion/unit mass are equal to that of control.²⁻⁷ Although normalization of wall stress, oxygen consumption and perfusion/unit mass under basal conditions exists, myocardial hypertrophy is associated with many adverse effects. Adverse effects on cardiac muscle include decreased contractility,⁸ increased collagen content,⁹ abnormal electrophysiologic properties^{10,11} and diastolic function.¹² Another important abnormality is the alteration in myocardial perfusion that is associated with LV hypertrophy. Many recent studies have supported several new concepts of perfusion abnormalities in the presence of LV hypertrophy. However, this review will concentrate on the effects of pressure-induced myocardial hypertrophy on coronary blood flow, vasodilator reserve, altered autoregulation and coronary artery occlusion.

Coronary blood flow: Nearly all studies in animal models of LV hypertrophy showed that when an increase in muscle mass stabilizes after the imposition of pressure load to the left ventricle, flow/gram of myocardium in the hypertrophied left ventricle was normal (Figure 1).^{2,3,6,13-22} The transmural distribution of resting LV perfusion usually was not altered significantly unless hypertrophy was severe (>75% increase in LV mass). In dogs with severe LV hypertrophy secondary to coarctation of the aorta, subendocardial flow was equal to or less than the subepicardial flow; the greatest flow occurs in the LV midwall layers.^{2,13,14,22}

Effect of tachycardia on coronary flow in left ventricular hypertrophy: In nonhypertrophied hearts, tachycardia induced by pacing (rate of 200 to 300 beats/min) increased coronary blood flow approximately 2-fold and the ratio of subendocardium to subepicardial flow usually decreased.^{2,18}

In the pressure hypertrophied left ventricle, flow increased with pacing, but in some models, the increase in

subendocardial perfusion was limited.^{2,23} These 2 studies showed the differences in coronary perfusion pressure between hypertrophy produced by arterial hypertension (in which coronary pressure was increased both in systole and diastole) and aortic banding (where coronary pressure was increased during systole but remained essentially normal during diastole). With increasing aortic diastolic pressure, transmural flow was normal; with normal aortic diastolic pressure, transmural flow was slightly impaired. However, in both situations in the dog, the effect of exercise on myocardial perfusion on the hypertrophied left ventricle was barely detectable even with the best technology.

Coronary vasodilator reserve: CORONARY VASCULAR RESISTANCE: Studies during maximal coronary vasodilatation have reported that minimal coronary vascular resistance is inappropriately high in animals with pressure-induced LV hypertrophy (Figure 2).^{3,6,16,24,25} Generally, coronary vascular resistance for the entire left ventricle was similar in normal and hypertrophied hearts and minimal coronary vascular resistance/gram increased. This implies that vascular growth has not kept up with the increase in myocardial muscle mass. Although the finding of increased minimal coronary vascular resistance in pressure-induced LV hypertrophy has been consistent, the magnitude of this abnormality was small.

Coronary vasodilator reserve: Wangler et al²⁵ have shown that coronary vascular growth can continue throughout a significant portion of a rat's life span. They found that prolonged periods of stable myocardial hypertrophy increased the coronary vasculature sufficiently to return coronary vasodilator reserve to normal levels (Figure 3). When the hypertrophy was more intense (50% increase in LV mass) the abnormality in coronary reserve persisted throughout a long segment of the animal's life span.

Recently, Tomanek et al²⁶ evaluated the effects of long-term LV hypertrophy secondary to renal hypertension. They found that in long-term (7 months) hypertrophy, coronary vasodilator reserve and minimal coronary vascular resistance returned toward normal levels,²⁶ which suggested that in this renovascular dog model, coronary angiogenesis was possible.

Coronary vasodilator reserve in patients with pressure-induced left ventricular hypertrophy: The mechanisms of angina in patients with aortic stenosis and normal coronary arteries have plagued clinicians for decades. In 1967, Fallen et al²⁷ presented evidence that coronary vascular reserve was decreased in patients with aortic stenosis and normal coronary arteries. The methods used by Fallen et al²⁷ were less than ideal. They

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used lactate and oxygen extraction using arterial and coronary sinus blood samples. In 1982, Marcus et al,²⁸ using a specially designed 20-MHz Doppler probe, measured the maximum velocity of coronary blood flow in the left anterior descending coronary artery at the time of elective open-heart surgery in 14 patients with aortic stenosis, LV hypertrophy and normal coronary arteries (Figure 4). They found the ratio of peak velocity of coronary blood flow after a 20-second occlusion to a resting velocity was decreased by >50% in patients with aortic stenosis, LV hypertrophy and normal coronary arteries. In addition, Doppler studies of an acute marginal branch of the right coronary artery showed only mild coronary vasodilator reserve abnormalities. These data suggested a selective and marked decrease of coronary reserve to the hypertrophied left ventricles in patients with severe aortic stenosis. These data further support the concept that the impairment of coronary vascular reserve was an important contributor to the pathogenesis of angina pectoris in patients with aortic stenosis, LV hypertrophy and normal coronary arteries. Immediately after partial relief of aortic valve obstruction, the coro-

nary vasodilator reserve in the left anterior descending coronary artery was not significantly improved, suggesting that extravascular compressive forces are not responsible for observed impairment of coronary dilator reserve.

Effects of hypertension and left ventricular hypertrophy on autoregulation of myocardial perfusion:

Autoregulation is the ability of a tissue to preserve blood flow over a wide range of blood pressures. Recently, Harrison et al²⁹ evaluated the effects of hypertension and left ventricular hypertrophy on the lower pressure limit for autoregulation in the coronary circulation. Using a chronically instrumented animal, these investigators lowered the perfusion pressure by inflating a balloon around the coronary artery to 75 and 40 mm Hg in both normal animals and animals with left ventricular hypertrophy secondary to renal hypertension (1 kidney, 1 clip). The authors expressed their results in terms of autoregulation gain. Autoregulation gain was defined as follows: autoregulation gain = $1 - [(\text{change in flow}/\text{initial flow})/(\text{change in pressure}/\text{initial pressure})]$.

FIGURE 1. Left ventricular perfusion/100 g of left ventricle in normal and hypertrophied hearts. Stable pressure-induced left ventricular hypertrophy (LVH [hypertensive + LVH]) does not increase flow/unit weight in left ventricle.

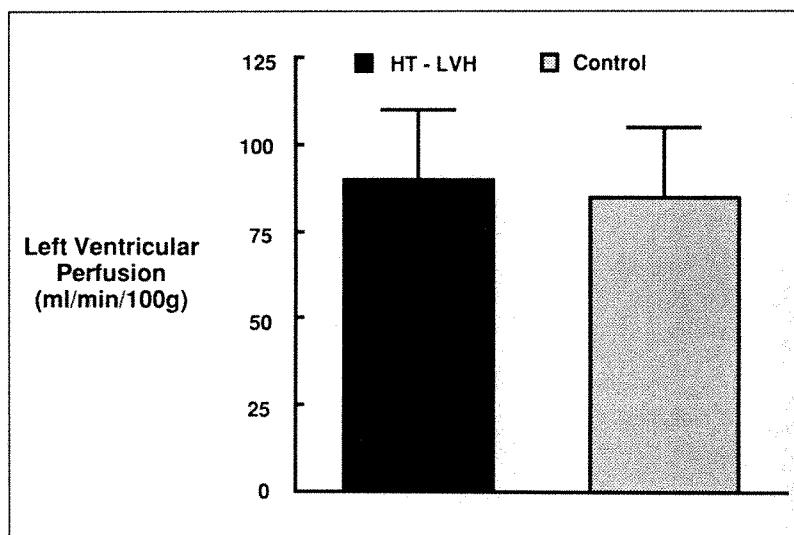
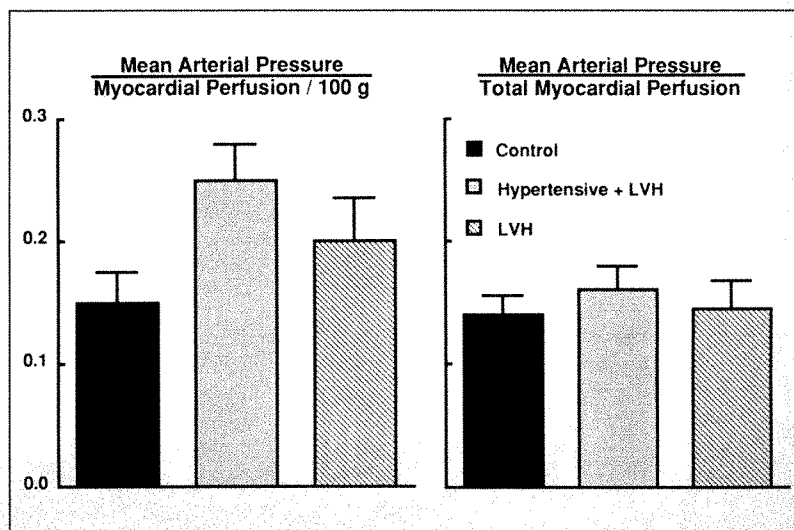


FIGURE 2. Left, minimal coronary vascular resistance expressed/100 g or (right) total left ventricle in the following 3 groups of dogs: control; hypertensive + left ventricular hypertrophy (LVH); and normotensive + LVH. Minimal coronary vascular resistance was calculated during maximal coronary blood flow produced by intravenous infusion of adenosine ($4.7 \mu\text{m}/\text{kg}/\text{min}$). In 2 groups of dogs with LV hypertrophy, minimal coronary vascular resistance/100 g was slightly increased (left). Minimal coronary vascular resistance for entire left ventricle was similar in all 3 groups of dogs (right).



Using this approach, an autoregulation gain of 1 indicates complete autoregulation, that is, as pressure was varied over a wide range, the flow remained constant. The absence of autoregulation was indicated by an autoregulation gain of 0. Their results suggested that autoregulation was impaired in the subendocardium of animals with hypertension and LV hypertrophy. These results are shown in Figure 5. Therefore, in the presence of long-standing hypertension and LV hypertrophy, rapid and aggressive treatment may predispose the patient to subendocardial ischemia in the absence of coronary stenosis.

Effects of coronary artery occlusion in animals with hypertension-induced left ventricular hypertrophy: Epidemiologic studies in patients with LV hypertrophy secondary to chronic arterial hypertension have shown a substantially increased risk for development of an acute myocardial infarction.³⁰ In addition, the incidence of sudden cardiac death was increased 3-fold and other complications of myocardial infarctions (such as heart failure) are more frequent than expected in patients with hypertension and LV hypertrophy.^{30,31} The increased risk for myocardial infarction was related in part to the increased prevalence of occlusive atheroscle-

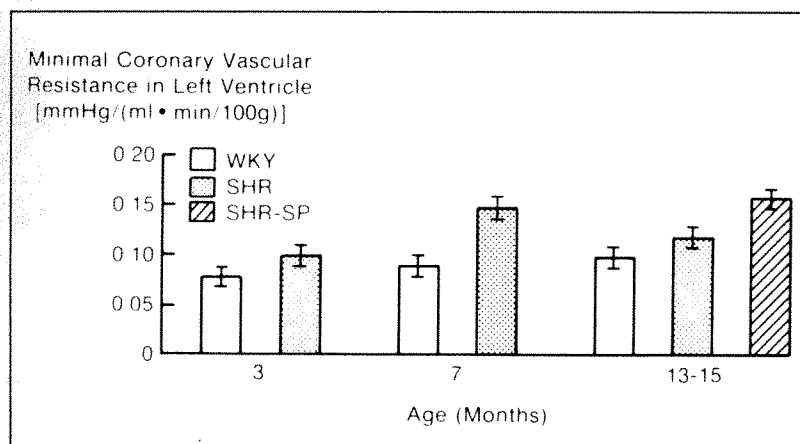


FIGURE 3. Interaction between age and coronary vascular growth in association with cardiac hypertrophy. In the rat species being examined (WKY and SHR), left ventricular hypertrophy is present at 3 months of age (SHR), maximal at 7 months of age and stable thereafter. SHR-SP have more severe hypertension and hypertrophy than SHR. Minimal coronary vascular resistance is calculated from maximal coronary flow and mean arterial pressure in awake, chronically instrumented rats. These data suggest that when left ventricular hypertrophy is not severe (SHR), given sufficient time, growth of coronary vasculature will keep pace with an increase in left ventricular mass.

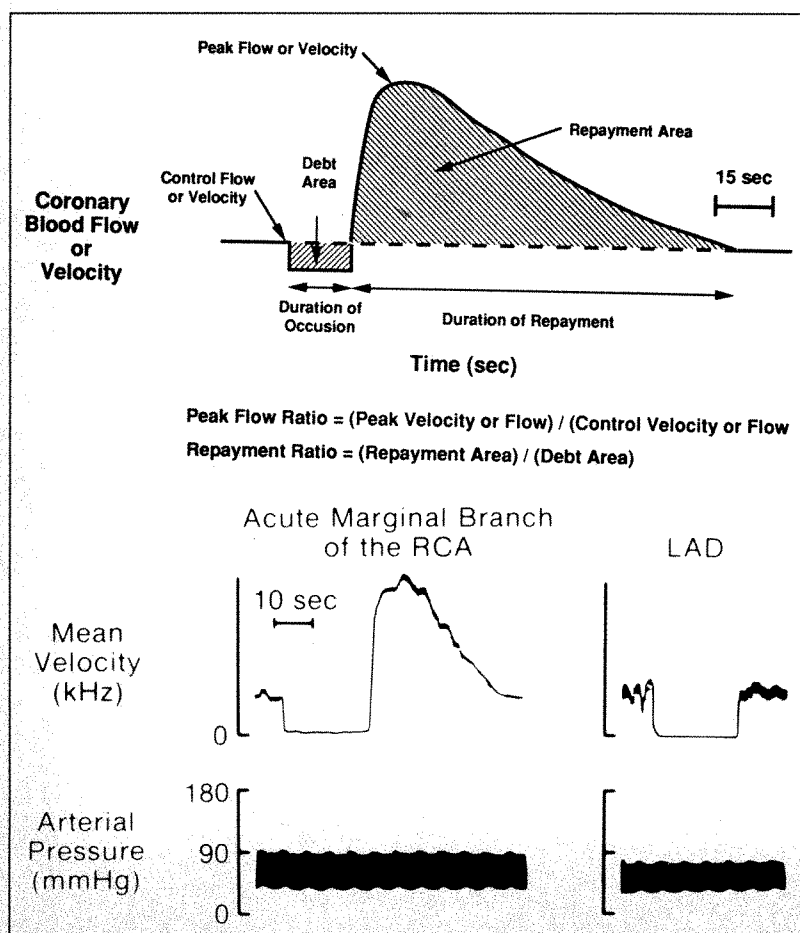


FIGURE 4. *Top*, standard measurements used to analyze reactive hyperemic responses. *Bottom*, coronary reactive hyperemic response in patient with severe aortic stenosis. These studies were obtained at time of open-heart surgery before cardiopulmonary bypass. Patient's right ventricle was of normal size; left ventricle was severely hypertrophied; coronary arteries were angiographically normal. Coronary reactive hyperemic response obtained from acute marginal branch of right coronary artery (RCA) was normal; coronary reactive hyperemic response obtained from left anterior descending (LAD) coronary artery was strikingly attenuated.

rotic coronary artery disease in hypertensive patients. These adverse effects of coronary artery occlusion could be related to hypertension, LV hypertrophy or a more extensive coronary atherosclerotic disease in patients with these concomitant conditions. To evaluate the interrelation between LV hypertrophy and infarction, Koyanagi et al³² studied the effect of coronary artery occlusion in awake dogs with LV hypertrophy secondary to renal hypertension (1 kidney, 1 clip). This model of hypertension and LV hypertrophy produces hypertension and LV hypertrophy similar to that seen in humans. These dogs underwent an abrupt occlusion of the left circumflex coronary artery (maintained for 48 hours) while conscious. During the 48 hours after coronary artery occlusion, 17% of control dogs died, whereas 54% of dogs with chronic arterial hypertension and LV hypertrophy died ($p < 0.01$; Figure 6). The area at risk (myocardium within the perfused territory of the occluded arteries) was determined using stereoscopic roentgenograms of barium-perfused coronary arteries. The area at risk expressed as percent of total LV mass was similar and normal in hypertrophied animals. In addition, the area at risk was not different between those animals that died prematurely and those animals that survived the entire period of coronary artery occlusion. When the area of infarcted tissue was related to the area of risk after coronary artery occlusion, the slope of the relation was similar in control and hypertensive animals, but the X intercept for zero infarct (risk region below which no infarction occurred) was shifted leftward in hypertensive animals (Figure 7). Thus, over the entire range of risk area studied, infarct size was increased for a given area at risk in animals with hypertension and LV hypertrophy compared to normal animals. Mean infarct size as a percentage of the area at risk was increased from 31% in normal dogs

to 54% in dogs with hypertension and hypertrophy ($p < 0.05$). In a separate study by Inou et al,³³ when the arterial pressures were returned to normal, acute coronary occlusion was no longer associated with increased

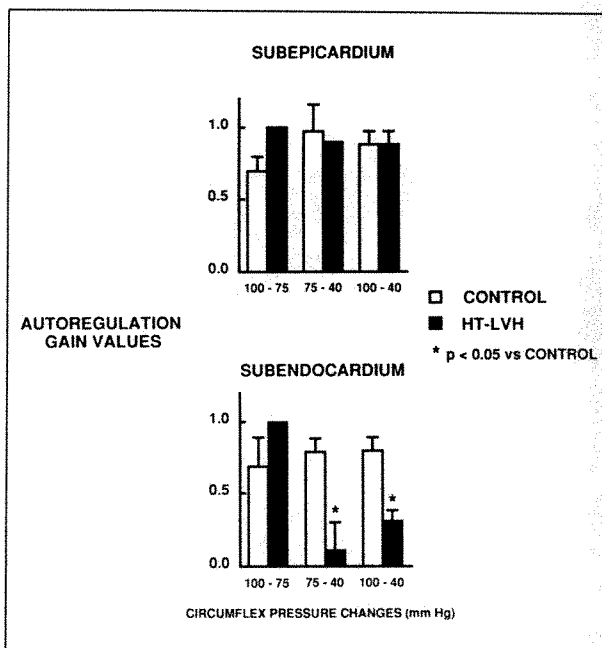
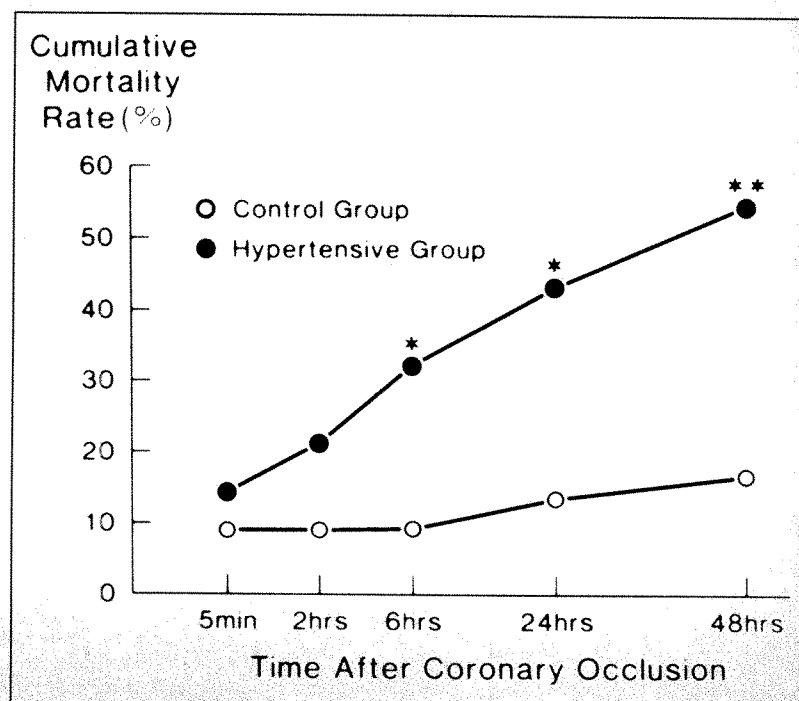


FIGURE 5. Comparison of autoregulation gain in normal animals and animals with hypertension and LV hypertrophy (HT-LVH) in subepicardium (top) and subendocardium (bottom) after decreases in perfusion pressure from 100 to 75, 75 to 40 and 100 to 40 mm Hg, respectively. An autoregulation gain of 1 is perfect autoregulation, whereas an autoregulation of a gain of 0 is no autoregulation. There is a significant decrease in the autoregulation gain (lack of autoregulation) of animals with HT-LVH only in subendocardium.

FIGURE 6. Effects of sudden coronary artery occlusion on mortality in normal dogs (control group) and hypertensive dogs with left ventricular hypertrophy (hypertensive group). * $p < 0.05$ versus control; ** $p < 0.01$ versus control.



mortality or increased infarct size despite decrease of arterial pressure reduction. These data suggested that hypertension, not LV hypertrophy, was the predominant factor responsible for increasing mortality and infarct size in animals with renal artery stenosis.

Recently, Dellsperger et al³⁴ performed studies to evaluate the wavefront of myocardial cell necrosis in animals with hypertension-induced LV hypertrophy. Both normal and hypertensive animals were subjected to coronary occlusions for periods of 1 and 3 hours. Mortality

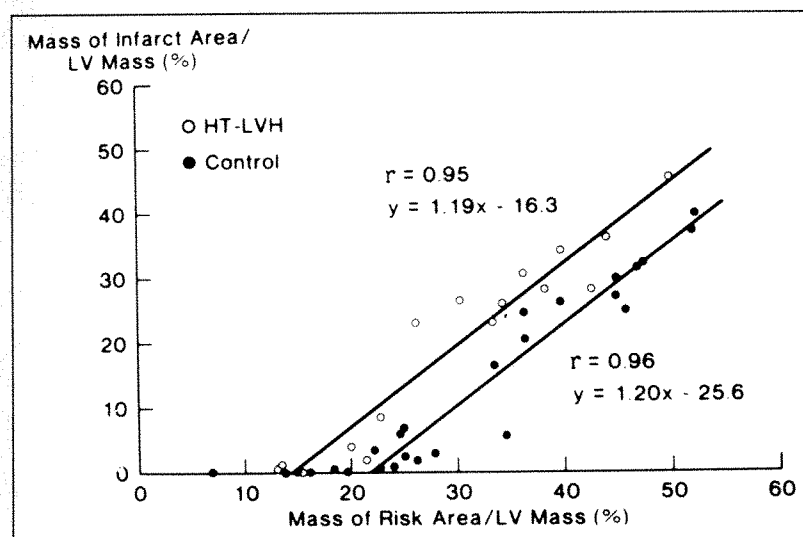


FIGURE 7. Effects of chronic hypertension (HT) and left ventricular hypertrophy (LVH) on infarct-risk relation. In this study, dogs were subjected to sudden coronary artery occlusion in the awake state. Forty-eight hours later, infarct size was determined by pathologic techniques and risk area determined by postmortem angiography. Over entire range of risk areas examined, dogs with HT-LVH had larger infarcts than control subjects.

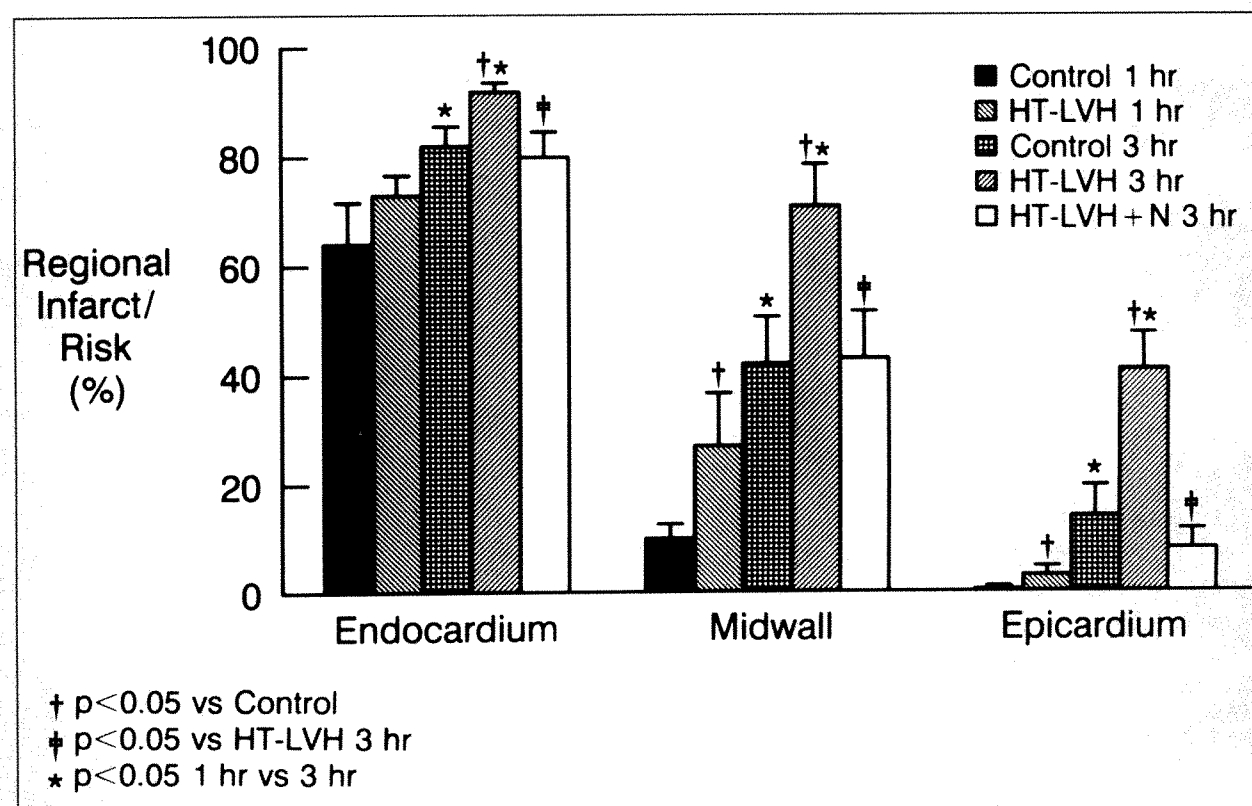
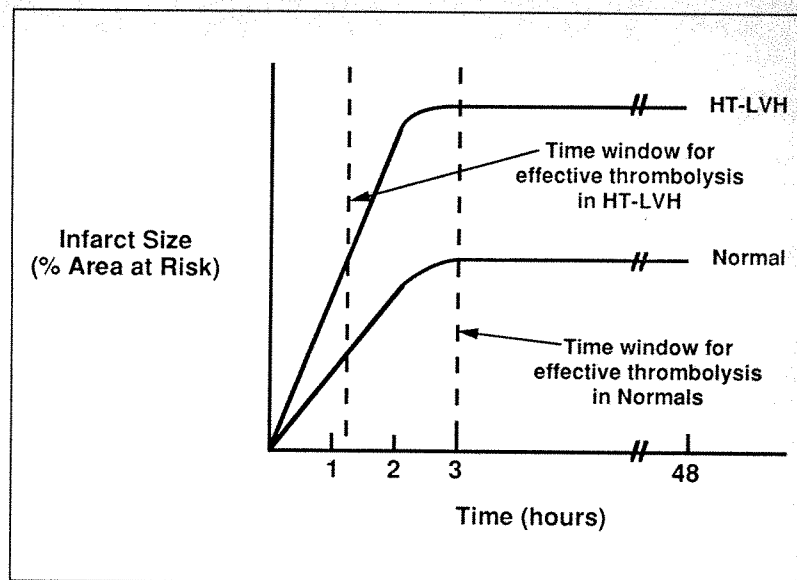


FIGURE 8. Effects of chronic hypertension and left ventricular hypertrophy (HT-LVH) on wavefront of myocardial necrosis. In this study, dogs were subjected to coronary artery occlusion of either 1 or 3 hours duration in the awake state. Infarct size was determined by triphenyltetrazolium chloride staining and risk areas were determined by postmortem angiography. Significantly more infarction occurred in the midwall and epicardial thirds of animals with HT-LVH after a 1-hour coronary artery occlusion. After a 3-hour coronary artery occlusion, significantly more infarction occurred throughout the entire left ventricle. These data suggest that the wavefront of necrosis is accelerated across the left ventricular wall in animals with HT-LVH. In another group of dogs with HT-LVH, nitroprusside (N) was infused 1 hour after coronary artery occlusion to return blood pressure to normal levels (HT-LVH + N). After a 3-hour total infarct, the infarct-to-risk relation was similar to that of control dogs after a 3-hour coronary artery occlusion. These data would suggest that manipulation of arterial pressure has striking effects on wavefront of myocardial cell necrosis.

FIGURE 9. This figure schematically shows results in Figure 8. Upper curve shows time course of infarction for animals with hypertension and left ventricular hypertrophy (HT-LVH). Bottom curve is time course of infarction in normal animals. Vertical dotted line on right shows time limit for reperfusion to decrease infarction by 50% in normal animals. HT-LVH shifts this time limit substantially to the left. Therefore, the time window for effective thrombolysis is markedly shortened by HT-LVH.



after sudden coronary artery occlusion was increased in the animals with hypertension and LV hypertrophy ($p < 0.05$). Infarct size expressed as a percentage of the area at risk was slightly greater in animals with hypertension and LV hypertrophy compared to normal animals after 1 hour of coronary artery occlusion ($p = 0.07$). After 3 hours of coronary artery occlusion, the infarct-to-risk ratio was also greater in animals with hypertension and LV hypertrophy ($p < 0.05$). The left ventricle was evaluated in terms of subendocardial, midwall and subepicardial thirds. The midmyocardial and subepicardial regional infarct-to-risk ratios were significantly greater in animals with hypertension and LV hypertrophy after 1 hour of coronary artery occlusion ($p < 0.05$). After 3 hours of coronary occlusion, the infarct risk ratios in each region of the myocardium were significantly increased in animals with hypertension and LV hypertrophy (Figure 8). The data suggested the wavefront of myocardial cell necrosis was accelerated in animals with hypertension and LV hypertrophy. Nitroprusside infused in dogs with hypertension and LV hypertrophy, after 1 hour of coronary artery occlusion to decrease blood pressure to normal levels, significantly decreased infarct size after 3 hours of occlusion from untreated animals with hypertension and LV hypertrophy. These data suggest that the wavefront of infarction is strikingly modulated by blood pressure. Figure 9 schematically shows these results and shows the potential effects on thrombolysis.

The above-mentioned studies on coronary artery occlusion³²⁻³⁴ suggested that hypertension, not hypertrophy, was the predominant factor responsible for the increased mortality and increased infarct size seen in animals with renal artery stenosis. These findings do not imply that hypertrophy alone would not be associated with deleterious response to the effects of acute coronary artery occlusion.

Based on these animal studies, the clinical implications of coronary artery occlusion in hypertensive patients may be summarized as follows. First, the mortality from coronary artery occlusion may be higher due to

both the increased incidence of sudden death and the increase in infarct size. Second, the window for thrombolysis appears to be shifted toward the left (Figure 9. To prevent 50% of myocardial necrosis, reperfusion needs to be instituted substantially earlier.) Finally, the use of a hypotensive agent (nitroprusside) early in the course of infarction may substantially decrease the size of resultant infarction and shift the window for thrombolysis back toward normal.

Summary: Many laboratories have provided evidence to support the concept that LV hypertrophy is associated with many significant coronary perfusion abnormalities. The decreased coronary flow reserve in the presence of LV hypertrophy is implicated as the mechanism of angina in patients with aortic stenosis and normal coronary arteries. The abnormal subendocardial autoregulation found in dogs may have important implications for the abrupt treatment of hypertension in patients with LV hypertrophy. The marked increase in mortality and the wavefront of infarction in dogs with hypertension and LV hypertrophy may have striking clinical implications for the salvage of myocardium in patients with chronic hypertension and LV hypertrophy during acute myocardial infarction.

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Association of Mitral Anular Calcium with New Thromboembolic Stroke and Cardiac Events at 39-Month Follow-Up in Elderly Patients

Wilbert S. Aronow, MD, Mordecai Koenigsberg, MD, Itzhak Kronzon, MD, and Hal Gutstein, MD

Mitral anular calcium (MAC) is a degenerative process common in elderly persons.¹⁻⁴ Nair et al⁵ reported 4.4-year follow-up data in 107 patients with MAC younger than 61 years of age and in 107 age- and sex-matched control subjects without MAC. During follow-up, their patients with MAC had a 15.5-times higher incidence of total cardiac deaths and a 5.0-times higher incidence of cerebrovascular events than control subjects. We are reporting the results from our prospective study of 976 patients older than 62 years of age. Our findings associate MAC with the development of new thromboembolic stroke and cardiac events at 39-month follow-up.

M-mode and 2-dimensional echocardiograms and 12-lead electrocardiograms with rhythm strips were recorded in a prospective study in 1,108 unselected elderly patients older than 62 years of age admitted to a long-term health care facility. Technically adequate M-mode and 2-dimensional echocardiograms of the mitral valve were recorded in 976 of 1,108 patients (88%). The 976 patients included 714 women and 262 men, mean age 82 ± 8 years (range 62 to 103).

M-mode and 2-dimensional echocardiograms of the mitral valve were obtained as previously described.^{4,6-8} MAC was diagnosed as previously described.^{4,6-8} Left atrial enlargement was diagnosed if the left atrial dimension plotted against age and body surface area exceeded the upper limit of the normal 95% prediction interval on a graph.⁹

Mean follow-up period was 39 ± 16 months (range 7 to 59). New cardiac events were diagnosed if the patient developed nonfatal or fatal myocardial infarction, primary ventricular fibrillation or sudden cardiac death. Data on other cardiac events such as congestive heart failure are available but not reported because these cardiac events were not included in the original design of this prospective study. Myocardial infarction was diagnosed as previously described.¹⁰ Primary ventricular fibrillation was defined as ventricular fibrillation documented by electrocardiogram in a clinically stable patient with cardiac disease unexpectedly having new cardiac symptoms. Sudden cardiac death was defined as an unexpected cardiac death in a patient with cardiac disease found dead within 1 hour of being clinically stable.¹¹

Thromboembolic stroke was diagnosed by a neurologist if a focal neurologic event occurred suddenly but without prolonged unconsciousness, nuchal rigidity, fever, pronounced leukocytosis or bloody spinal fluid.¹² The focal neurologic signs of ischemic stroke were ex-

TABLE I Prevalence of Left Atrial Enlargement and Atrial Fibrillation in Elderly Patients With and Without Mitral Anular Calcium

	MAC (n = 526)		No MAC (n = 450)		p Value
	No.	%	No.	%	
Left atrial enlargement	218	41	77	17	<0.001
Atrial fibrillation	90	17	41	9	<0.001

MAC = mitral anular calcium.

TABLE II Association of Mitral Anular Calcium with New Thromboembolic Stroke in Elderly Patients with Atrial Fibrillation and Sinus Rhythm

	Thromboembolic Stroke				p Value
	MAC		No MAC		
	No.	%	No.	%	
Atrial fibrillation	45/90	50	14/41	34	NS
Sinus rhythm	59/436	14	38/409	9	NS
All patients	104/526	20	52/450	12	<0.001

NS = not significant; other abbreviation as in Table I.

NS = not significant; other abbreviation as in Table I.

plained by loss of function in a restricted area of the brain corresponding to a particular vascular territory. Thromboembolic stroke was also confirmed by computerized axial tomography in 147 of 156 patients (94%). Chi-square analyses were used to analyze data.

MAC was present in 402 of 714 women (56%) and in 124 of 262 men (47%), $p < 0.02$. No MAC was present in 138 of 262 men (53%) and in 312 of 714 women (44%), $p < 0.02$. The mean age was 84 ± 8 years in patients with MAC and 81 ± 8 years in patients without MAC (difference not significant). Table I shows the prevalence of left atrial enlargement and of atrial fibrillation (AF) in patients with and without MAC. Table II states the association of MAC with new thromboembolic stroke in patients with AF, in sinus rhythm and in all patients. Table III shows the association of MAC with new cardiac events in patients with AF, in sinus rhythm and in all patients. Bacterial endocarditis developed in 14 of 526 patients (3%) with MAC and in 3 of 450 patients (1%) without MAC, $p < 0.02$.

Left atrial enlargement was 2.4-times more prevalent and AF 1.9-times more prevalent in patients with MAC than in patients without MAC. Other studies have also shown a higher prevalence of left atrial enlargement^{1,4,5,13} and of AF^{1,2,4,5,13} in patients with MAC. MAC also causes mitral regurgitation^{1,2,7,8,13} and mitral stenosis^{1,7,8,13} and is more prevalent in patients with valvular aortic stenosis^{1,2,6,13-15} and hypertrophic cardiomyopathy.¹⁶⁻¹⁸

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TABLE III Association of Mitral Anular Calcium with New Cardiac Events in Elderly Patients with Atrial Fibrillation and Sinus Rhythm

	Cardiac Events				p Value
	MAC		No MAC		
	No.	%	No.	%	
Atrial fibrillation	62/90	69	22/41	54	NS
Sinus rhythm	157/436	36	106/409	26	<0.005
All patients	219/526	42	128/450	28	<0.001
Abbreviations as in Tables I and II.					

Abbreviations as in Tables I and II.

Nair et al⁵ demonstrated at 4.4-year follow-up that patients with MAC younger than 61 years of age had a 5.0-times higher incidence of cerebrovascular events than control subjects. Data from our prospective study in patients with MAC older than 62 years of age showed that patients with MAC were 1.7-times (1.8 times in men and 1.7 times in women) more likely to develop thromboembolic stroke during 39-month follow-up than patients without MAC. Antithrombotic agents were not administered to patients in this study because they had MAC.

Nair et al⁵ also found at 4.4-year follow-up that patients with MAC younger than 61 years of age had a 15.5-times higher incidence of total cardiac death than control subjects. Data from our study showed that patients with MAC older than 62 years of age were 1.5-times (1.6 times in men and 1.4 times in women) more likely to develop myocardial infarction, primary ventricular fibrillation or sudden cardiac death during 39-month follow-up than patients without MAC.

Nair et al⁵ did not find a higher incidence of bacterial endocarditis in patients with MAC than in control subjects. We found a higher incidence of bacterial endocarditis in our patients with MAC and, therefore, favor prophylactic antibiotics in patients with MAC according to American Heart Association guidelines.¹⁹

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Fractal Clustering of Ventricular Ectopy in Dilated Cardiomyopathy

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Chaos theory, a term that includes the overlapping fields of fractal geometry and nonlinear dynamics, can provide new insights into cardiovascular pathophysiology.^{1,2} Based on the hypothesis that the pattern of ventricular ectopy in patients with heart disease may provide clues to prognosis, we have developed a method that uses fractal geometry³ to quantify the degree of clustering present in ventricular arrhythmias. This method measures a "fractal dimension," symbolized by "D," which

can range from 0 in the case of extremely high clustering to 1 in the case of ectopy that is uniformly distributed in time. Among patients with dilated cardiomyopathy who have frequent and complex ventricular arrhythmias, the presence of clustered ectopy identifies a subset of patients with a particularly poor prognosis.

The fractal dimension can be estimated by use of the correlation integral.⁴ This function is created as follows: (1) take an object that is described by a defined number of points; (2) identify all of the possible pairs of these points; (3) make a list of these pairs and for each note the distance separating the 2 points that make up the pair; (4) take a given distance and count the number of pairs

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separated by this distance or less; and (5) repeat this for a variety of different distances. The result is a function that relates the number of pairs of points separated by less than any given distance to that distance. The slope of the line relating the log of the number of pairs to the log of the distance is the "correlation dimension," or fractal dimension (D), of the object.

The dimension D is an estimate of the extent to which accumulation of data pairs is dependent on the scale of measurement. Accordingly, D is inversely related to the degree of clustering of the points that make up the object. If the points are spread out homogeneously, the number of pairs of points separated by less than any given distance will increase in proportion to the distance. If those points are distributed over a line (such as a time axis), D will be equal to 1. However, if the points are densely clustered, then beyond a critical distance the number of pairs will no longer increase. Under these conditions, the number of pairs of points will remain constant, irrespective of distance, and D will approach 0. Ventricular premature complexes can be considered as discrete events in time. By using the correlation dimension algorithm with an appropriate time scale, we can estimate the degree of uniformity or clustering that is present in the pattern of a ventricular arrhythmia.

To evaluate the applicability and prognostic value of ventricular arrhythmia clustering determined by fractal analysis, we retrospectively examined ambulatory electrocardiographic data in 18 patients with severe ischemic and nonischemic dilated cardiomyopathy who had been followed from the time of monitoring for as long as 4 years. Short-term survival is poor in this population, and mortality in these patients has been correlated with the

TABLE I Fractal Dimension and Arrhythmia Frequency and Complexity Characteristics During 200 Ectopic Beat Analysis Interval in Patients with Dilated Cardiomyopathy

Pt	D	VPCs/hr	Peak Lown Grade	Longest VT Run	Total VT Beats
MP	0.59	201	4B	3	3
JM	0.64	103	4B	3	6
NS	0.80	19	4B	6	6
RB	0.81	28	4A	0	0
IN	0.87	82	4A	0	0
AM	0.88	27	4A	0	0
AF	0.88	239	4B	3	12
VW	0.90	383	3	0	0
JR	0.90	50	3	0	0
CS	0.93	47	4A	0	0
SC	0.93	154	4B	3	3
DG	0.93	29	4B	5	10
JP	0.94	55	4A	0	0
GN	0.97	47	3	0	0
MK	0.97	64	4A	0	0
JI	0.98	24	4A	0	0
RM	0.99	164	4B	3	6
JS	0.99	18	3	0	0

D = fractal dimension; VPCs = ventricular premature complexes; VT = ventricular tachycardia.

magnitude of ventricular dysfunction and with the presence and frequency of repetitive ventricular arrhythmias, including ventricular couplets and nonsustained ventricular tachycardia.^{5,6}

There were 13 men and 5 women whose ages ranged from 36 to 68 years. Patients who were not in sinus rhythm and patients who had <200 ventricular premature complexes during the 24-hour period of monitoring were not included in the analysis. Follow-up data were obtained for all patients, but 2 were lost to further follow-up, before death, at 4 and 23 months after entry. One surviving patient underwent cardiac transplantation 27 months after entry and was censored at that time in the survival analysis. The remaining 14 patients were followed to time of death. Two patients are alive at the present time.

Ambulatory electrocardiographic recordings of bipolar leads CM₁ and CM₅ were scanned (Avionics Trendsetter) using visual complex superimposition methods as well as direct visual confirmation for identification and timing of consecutively detected ventricular premature complexes. Complex ventricular arrhythmias were common in this population. According to the Lown grading system,⁷ there were 11 patients with ventricular tachycardia (grade 4B, ≥ 3 sequential ventricular premature complexes), 6 patients with ventricular couplets (grade 4A, 2 sequential ventricular premature complexes), and 1 patient with only multiform single ventricular premature complexes (grade 3) as the most advanced arrhythmia during the entire recording period.

To within 1-second accuracy, the time of the first 200 ventricular premature complexes in each recording was listed. The mean frequency of ventricular premature complexes, the peak grade of arrhythmia complexity and the number, length and total complexes involved in episodes of ventricular tachycardia were determined during this period of analysis for each patient, separate

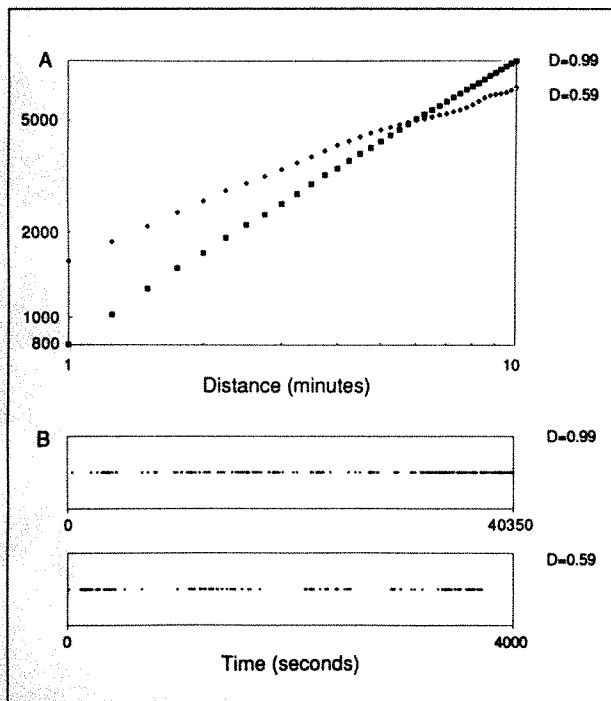


FIGURE 1. Correlation curves (A) and raw data (B) for 2 representative patients. Dimension (D) is the slope of the correlation plot.

from the overall peak grading obtained during the entire recording. The number of pairs of ectopic complexes that could be formed within time (t) of one another was determined for t values ranging from 1 to 10 minutes. From these data, the fractal dimension (D) was calculated as the absolute value of the slope of the regression relating the log of the total number of ectopic complexes that can be paired within time intervals from 1 to 10 minutes to the log of the corresponding time interval.

Representative correlation curves from 2 patients are shown in Figure 1. The model provided a close linear fit of the regression data for all patients, with $r^2 > 0.98$ in each case. Calculated fractal dimension ranged from 0.59, for the most highly clustered case, to 0.99 for the most uniform. D was not significantly correlated with either frequency of ectopy, peak grade of ectopy or total number of ventricular tachycardia complexes during the period of analysis (Table I), which extended for 200 ectopic complexes in each case, or with the peak grade of ventricular ectopy found during the entire period of ambulatory recording in each patient.

To determine the confidence limits for D for a uniform random distribution with similar characteristics, we performed 20 simulations (using a computerized random number generator, GFA Basic 3.0, GFA Systemtechnik, 1988) based on the mean interectopic intervals found in our patient population. The mean value for D in these simulations was 0.98. The 95% confidence limits, as obtained by the Student t test, were 0.90 to 1.06. In over one-third (7 of 18) of our patients, D was below the lower confidence limit found for the uniform random distribution. This observation suggests that ventricular premature complexes do not always behave as random events, but can be demonstrably nonuniform over time.

The prognostic value of the calculated fractal dimension D was examined by stratification of the population into 2 groups at the median value of 0.92. Patients with $D \leq 0.92$ formed the "clustered group," and patients with

greater D values formed the "uniform group." Survival curves, constructed using the product-limit estimate of Kaplan and Meier, revealed a striking difference in short-term prognosis for patients separated according to the median fractal dimension (Figure 2). Patients in the clustered group had markedly lower survival than did patients in the uniform group at 6 months (56 vs 100%), with differences closing by 24 months (44 vs 46%). Survival curves were significantly different ($p < 0.001$) by the method of Mantel and Haenszel. The same trend was found when the patients were divided into tertiles or quartiles. These results were not explained by higher mortality in patients who had ventricular tachycardia (grade 4B) during the total period of ambulatory recording. When these 11 patients were separately examined, 6-month survival was significantly reduced when clustered ectopy was present (57 vs 100%, $p < 0.02$ by Mantel-Haenszel testing), and a similar trend was found in the small group of 6 patients with ventricular couplets (grade 4A) as the peak complexity grade when separated according to fractal dimension (50 vs 100%, $p = 0.08$).

Our findings demonstrate that fractal analysis of ventricular ectopy is feasible, that ventricular arrhythmias are often nonuniformly distributed, that the fractal dimension appears to be independent of traditional quantification of arrhythmia frequency and complexity and that this dimension can be related to mortality among a small group of high-risk patients with dilated cardiomyopathy. Our data do not address whether the fractal dimension is independent of ventricular performance, which is a strong determinant of survival in heart failure.⁶ The absence of hemodynamic data in our test population limits comparison of ventricular function in our groups with uniform and clustered ectopy, and this requires prospective evaluation. In addition, larger numbers of patients are required to determine possible differences in prognostic value that might be based on the specific etiology of heart failure, and the value of fractal analysis in

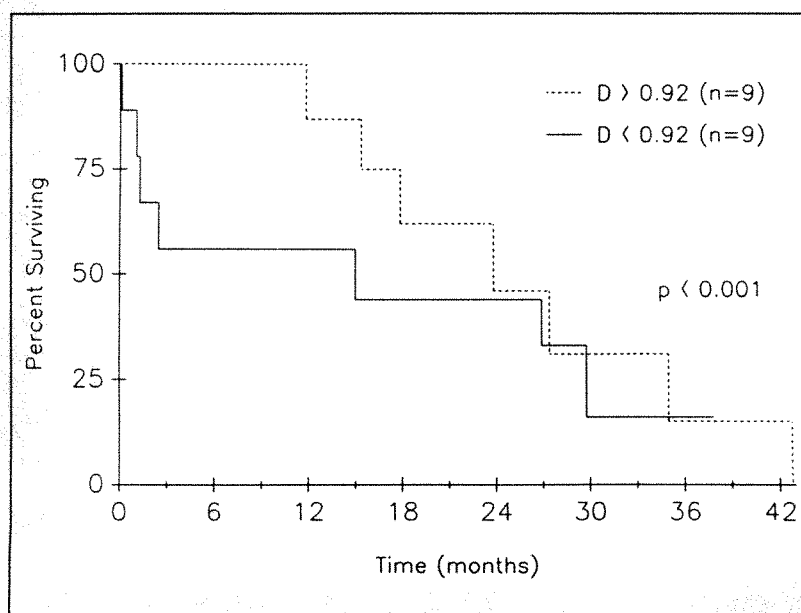


FIGURE 2. Product-limit estimate of survival in dilated cardiomyopathy (Kaplan-Meier curve) as a function of dimension of ventricular ectopy: $D \leq 0.92$ = "clustered"; $D > 0.92$ = "uniform".

other forms of disease requires specific testing. With these limitations in mind, however, our findings suggest that exploration of the fractal distribution of ventricular arrhythmias may provide future useful insights into the mechanism and prognosis of disease.

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Coronary Artery Spasm After Cardiac Transplantation

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Coronary artery spasm has been shown to play a role in exercise-induced angina,¹ unstable angina, acute myocardial infarction and sudden death.² The exact mechanisms of coronary artery spasm are poorly understood. Humoral,³ neural⁴ and endothelial⁵ mechanisms have been implicated. Cardiac denervation after transplantation coupled with immunologic damage to the endothelium⁶ can potentially alter the regulation of coronary vascular tone through loss of direct neural control⁷ as well as altering the response to humoral factors due to denervation hypersensitivity.⁸ Although surgical cardiac

denervation has been proposed as a form of treatment for patients with severe coronary spasm,⁹ the results are variable and coronary spasm has been documented after cardiac transplantation.¹⁰⁻¹² The exact causes, frequency and clinical presentation of this phenomenon have not been adequately defined, particularly in relation to accelerated coronary sclerosis and long-term prognosis. To clarify some of these issues, we discuss 4 cardiac transplant recipients with documented severe coronary spasm.

From 1980 to 1989, 667 orthotopic cardiac transplants have been carried out at Harefield Hospital. Annual reinvestigation, including coronary angiography, is routinely performed. Standard angiographic procedures using the Judkins technique have been adopted using 3 to 5 ml per injection of nonionic medium. All patients are maintained on immunosuppression of cyclosporine A,

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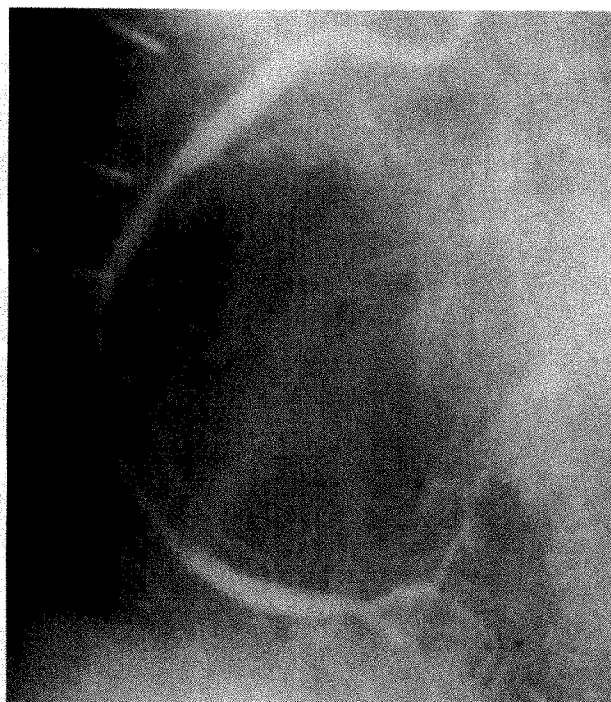


FIGURE 1. Angiographic appearance of right coronary artery in patient 1 during an episode of demonstrated spasm.

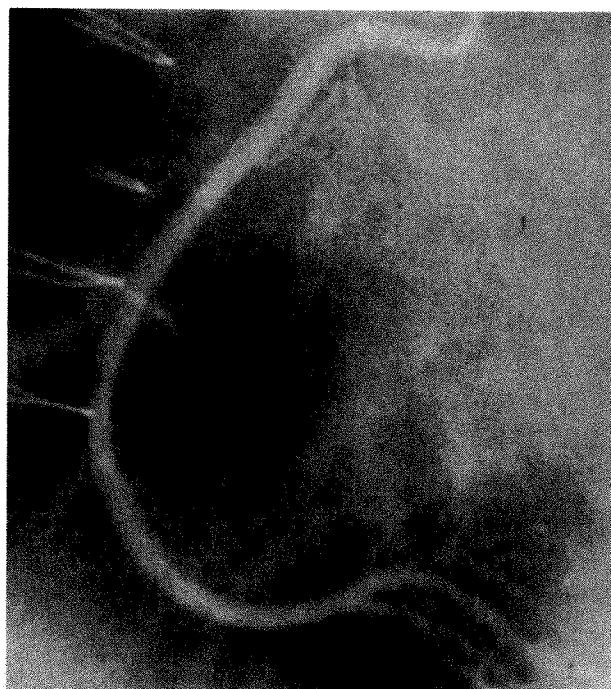


FIGURE 2. Right coronary artery in patient 1 after infusion of isosorbide dinitrate after demonstrated spasm.

TABLE I Relevant Clinical Details and Results of Investigations

	Patient 1	Patient 2	Patient 3	Patient 4
Patient age, sex and pretransplant diagnosis	14 M Diffuse interstitial fibrosis	35 M Ischemic cardiomyopathy	48 M IDC	39 M IDC
Donor age (yrs) and sex	31 F	36 M	32 M	33 M
Ischemic time (min)	225	239	80	135
Mode of presentation of coronary spasm	Collapse during exercise test with asystole	Chest pain at rest followed by bradycardia, ST elevation and asystole	Hypotension with ST elevation during coronary angiography	Inferior T wave changes on exercise testing
Dizziness and/or syncope	0	0	+	+
ST change on exercise test	+(†)	+(†)	0	+(‡)
Arrhythmia on 24-hour tape	0	0	0	Sinus bradycardia
Coronary artery narrowed > 75% at angiography				(Segmental)
RCA	+	0	+	+ spasm)
LAD	+	+	0	0
LC	0	+	0	0
Coronary spasm by ergonovine provocation	0	+	0	+(Right)
Rejection at time of spasm (endomyocardial biopsy)	0	0	0	0
Permanent ECG changes	Q waves	0	0	0

ECG = electrocardiogram; IDC = idiopathic dilated cardiomyopathy; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery.

the dose of which is adjusted to maintain a blood level of 150 to 250 ng/liter, and azathioprine, given at a dose of 2 mg/kg.

Four patients had documented severe coronary spasm at angiography as well as clinical and/or electrocardiographic features. Table I lists donor details and results of routine investigations as well as the relevant clinical features in each patient. All patients went on to develop diffuse coronary artery disease affecting the 3 main coronary arteries and their principle branches within 1 year of the diagnosis of spasm. Only 1 of these patients is still alive.

The patients described demonstrate that coronary artery spasm may occur after cardiac transplantation and may have an important influence on the clinical course. In patients 1 and 3, severe spasm was observed at angiography and reversed by intracoronary isosorbide dinitrate. It is likely that in patient 1, spasm was responsible for the inferior infarct and cardiac arrest. In patients 2 and 4, coronary spasm was confirmed by intracoronary ergonovine provocation.

All 4 patients had dizzy spells or syncope which may have been related to episodes of spontaneous coronary spasm. These symptoms were related to exertion and in 2

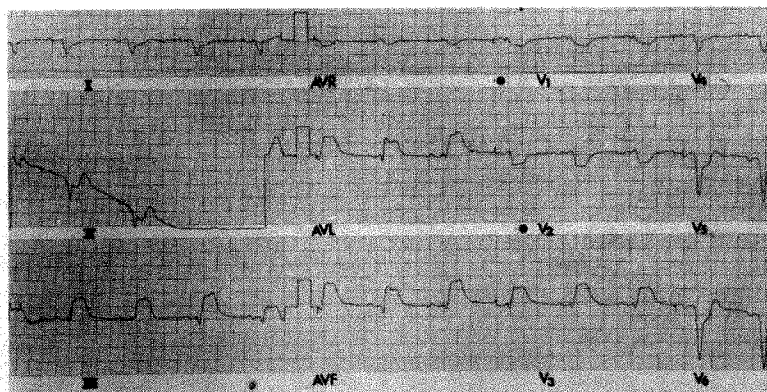


FIGURE 3. Electrocardiogram of patient 2 during an episode of suspected coronary spasm, showing widespread ST-segment change.

patients, the typical symptoms were followed by collapse on treadmill exercise testing. Sudden death occurred in 3 patients, suggesting that an acute arrhythmia may have been the causative factor even though 24-hour tape monitoring was negative. In the 2 patients in whom an autopsy was available (patients 1 and 4), severe coronary artery disease was demonstrated but coronary thrombus was absent. Patient 2 had fixed coronary narrowing at sites where spasm was observed.

There have been previously published case reports of coronary artery spasm after cardiac transplantation,¹⁰⁻¹² of which 1 case may have been catheter provoked.¹³ In all cases of spontaneous spasm in transplant patients, there are common features. Electrocardiographic ST-segment change and syncopal episodes are a consistent feature. Sudden death occurs and there is an association with the development of coronary artery disease that is rapidly progressive. There was histologic evidence at autopsy of chronic rejection in 2 of our cases and also in the patient reported by Cattani,¹¹ suggesting that this may be an important association.

There are similarities between the coronary artery spasm in these patients and the well characterized spasm recognized in nontransplanted coronary arteries.¹ In these cases, there is a well documented association with angina, acute myocardial infarction and sudden death.² In addition, coronary spasm in native coronary arteries may be an antecedent to the later development of fixed coronary artery disease.¹⁴ This relation may apply in cardiac transplant recipients.

It has been suggested that coronary artery spasm may be secondary to alpha-adrenergic sympathetic stimulation.¹⁵ Surgical denervation and autotransplantation have therefore been used to treat this condition,⁹ but the results have been inconsistent and variable suggesting that this is unlikely to play an important role in the pathogenesis of coronary artery spasm. None of our patients had evidence of reinnervation on physiologic testing and this is in keeping with a recent anatomic study con-

cluding that myocardial innervation is unlikely to be restored in transplanted human hearts.¹⁶

Local nonspecific hypersensitivity, rather than a specific agonist-receptor interaction, has been suggested as the mechanism of spasm in variant angina.¹⁷ In cardiac transplant recipients, denervation may remove the autonomic neural control mechanisms governing coronary tone and vessels may therefore be hypersensitive to local vasoconstrictor stimuli. This nonspecific local hypersensitivity may be an important mechanism. However, it is likely that more than 1 mechanism is involved in the pathogenesis of coronary vasoconstriction and spasm.¹⁸

We have used ergonovine maleate to provoke spasm as this is the most reliable and consistent inducer of vasospasm in patients with variant angina in whom there appears to be focal hypersensitivity to the drug.¹⁹ Early atherosclerotic change in coronary arteries may enhance the segmental vasoconstriction of these arteries in response to ergonovine.⁷ Ergonovine has been suggested to act by a direct local action²⁰ and may have stimulatory effect on the endothelium with the release of endothelium-derived relaxing factor.^{21,22} In patients with coronary spasm, endothelial dysfunction may result in the lack of release of endothelium-derived relaxing factor with only a vasoconstrictor effect of the drug.

The most important question raised by these patients is the possible association of coronary spasm with the development of accelerated coronary sclerosis.²³ The incidence of accelerated coronary sclerosis in cardiac transplant recipients is as high as 40% by 2.5 years.²⁴ The course of the patients described was poor. The deaths were within 2 years after transplantation and the coronary artery disease was particularly "aggressive" when compared with the incidence and progression of coronary

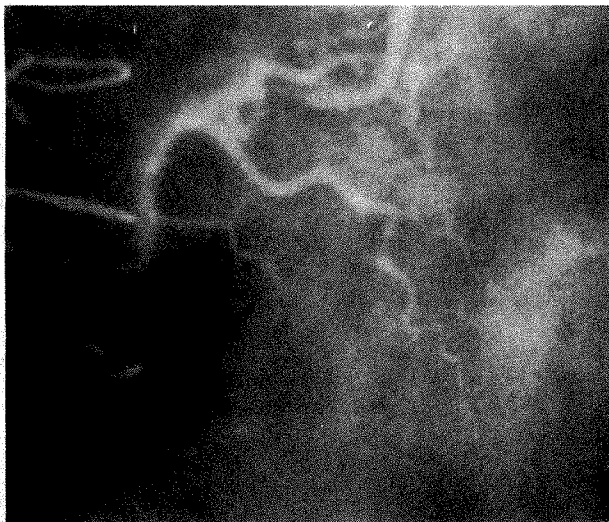


FIGURE 4. Angiographic appearance of right coronary artery in patient 3 during an episode of demonstrated spasm.



FIGURE 5. Right coronary artery in patient 3 after infusion of isosorbide dinitrate after demonstrated spasm.

disease at this institution. By the end of 1989, 12 of 268 patients (4.5%) had significant coronary artery disease and of these, only 1 had died within 2 years (unpublished data).

It has been suggested that catheter-induced spasm is related to spontaneous spasm.²⁵ We have noted at least 6 cases of catheter tip spasm in transplant recipients since 1980, but none had significant fixed coronary artery disease.

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Transcatheter Occlusion of High Flow Blalock-Taussig Shunts with a Detachable Balloon

Marc Gewillig, MD, Luc Van der Hauwaert, MD, and Wim Daenen, MD

Trascatheter occlusion of Blalock-Taussig shunts has been reported.¹⁻⁴ However, because of specific features of these shunts—such as common lack of distal stenosis and abundant, high velocity, turbulent blood flow—the reported procedures were difficult and cumbersome, and the final result was frequently suboptimal. We evaluated the feasibility and effectiveness of gold-valve detachable balloons for occluding high flow Blalock-Taussig shunts.

A modified Blalock-Taussig shunt (4 to 6 cm of 6 mm Gore-Tex) was created in 8 mongrel dogs (weight 18 to 29 kg, mean 21). When reevaluated 4 to 6 weeks after surgery, there was evidence of a significant shunt because the pulse pressure had increased from 30 ± 4 to 60 ± 8 mm Hg and the left ventricular end-diastolic volume

had increased by $55 \pm 24\%$. The shunt was approached from the brachial artery in order to reach it in an obtuse angle. An 8Fr delivery catheter was advanced into the shunt over a previously positioned guidewire. A gold-valve detachable balloon (deflated 2.7×1.4 mm, fully inflated 14.7×7.8 mm, Ingenor) was slipped over a 2.2Fr on a 3Fr carrier catheter, which was previously slid through a 5Fr guiding catheter. The balloon was positioned proximally in the shunt and inflated swiftly with 0.5 ml of diluted (1:2) contrast medium. Slow inflation of the balloon resulted in significant displacement into the pulmonary artery: the 3Fr carrier catheter was very stretchable.

The use of a tuberculin syringe, however, made nearly instantaneous inflation of the balloon possible. Despite abundant and high velocity (>4 m/s) blood flow, the connection between the nozzle and the valve did withstand the turbulent flow in the shunt and accurate positioning of the balloon was obtained in all dogs. Deflation and repositioning were possible until the balloon was detached with gentle traction on the 3Fr catheter while

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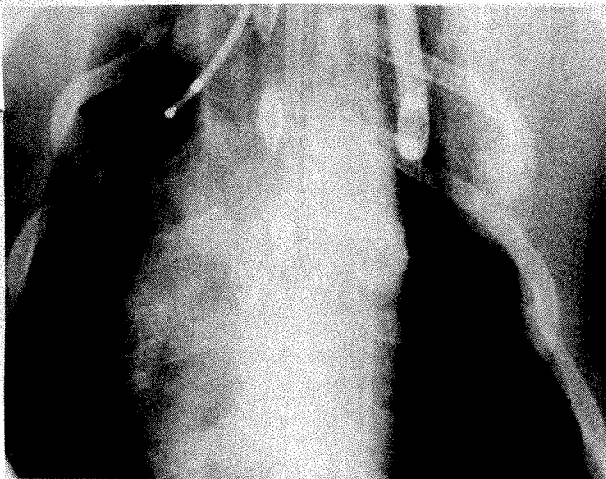


FIGURE 1. Selective contrast injection at the systemic end of a modified Blalock-Taussig shunt demonstrates total occlusion after release of a goldvalve balloon.

securing the position of the balloon with the 5Fr catheter. Inadvertent release of the balloon never occurred. Total occlusion, as demonstrated by a contrast injection at the systemic end of the shunt (Figure 1), was obtained in all dogs. Fluoroscopic control studies after 1 hour, 1 day and 1 and 4 weeks revealed no migration or deflation of the balloon. Antibiotic coverage was maintained for 24 hours after the procedure; there were no infectious complications. Pathologic examination in all dogs 1 month after occlusion demonstrated that the shunt was sealed off by endothelium at both ends (Figure 2). Late leakage of the balloon would therefore have had no hemodynamic repercussion. No balloon protruded into the pulmonary or subclavian artery.

Indications for percutaneous closure of a Blalock-Taussig shunt include residual shunts after attempted surgical ligation, simplification of subsequent surgery if a shunt is difficult to reach and does not constitute the sole pulmonary blood flow, or shunts in patients with pulmonary atresia and intact ventricular septum, where sufficient antegrade blood flow has developed after right ventricular outflow reconstruction, making the shunt useless or even detrimental.

Perry et al⁴ reported on 13 procedures where total occlusion of a Blalock-Taussig shunt was attempted with Gianturco coils. By using 1 to 5 coils, occlusion was complete in 6 patients but partial in 7. In 1 other patient where partial occlusion was intentional, severe hemolysis developed. In 3 patients there was an embolization of the coil to the pulmonary artery. Similar problems have been reported by other groups using either Gianturco coils or detachable balloons.^{1,3} Clearly, these difficulties are related to the specific anatomy and physiology of the shunt, in particular, the common lack of a distal stenosis and the abundant, high velocity, turbulent blood flow. To promote clotting and prevent pulmonary artery emboliza-

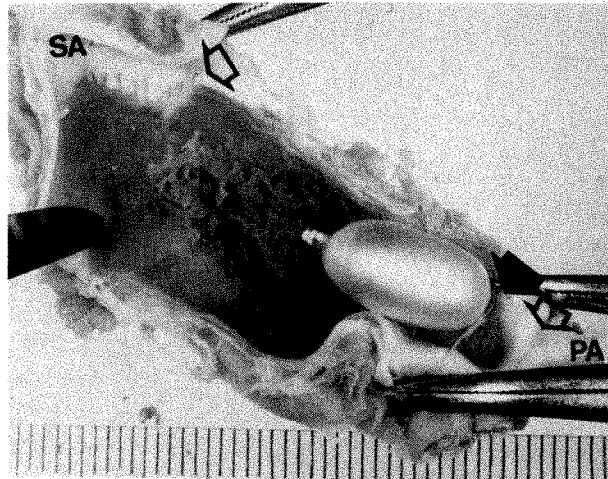


FIGURE 2. Longitudinal section of a modified Blalock-Taussig shunt excised 1 month after balloon occlusion. The balloon is well contained within the shunt (open arrows = suture line). The pulmonary end is sealed by a thin membrane (closed arrow). The membrane at the systemic end is not well visualized. PA = pulmonary artery; SA = subclavian artery; T = thrombus. Metric scale.

tion, temporary inflation of an additional balloon catheter in the pulmonary or systemic artery has been advocated to diminish blood flow through the shunt during the procedure.^{3,4}

We report our experience with occluding modified Blalock-Taussig shunts using a goldvalve detachable balloon. The valve connection allows easy mounting of the balloon on the catheter system, but still offers enough resistance to withstand the turbulent high flow of a Blalock-Taussig shunt. Inadvertent release, which has been reported with other balloon devices,³ never occurred. Late leakage of the balloon is very rare, allowing the use of diluted contrast instead of silicone. Balloons can be made in different sizes and shapes for different vessels. A major advantage of a balloon delivery system over the Gianturco coils is that until the balloon is released, the whole procedure can easily be undone. Also, this technique always results in immediate and complete occlusion of the shunt.

We conclude that a goldvalve detachable balloon is a safe and effective technique for total occlusion of a high flow, high velocity, modified Blalock-Taussig shunt.

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CASE REPORT

Distension of the Oblique Pericardial Sinus in Tamponade due to Loculated Posterior Pericardial Effusion

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Tamponade is an uncommon yet correctable complication of pericardial effusions in patients recovering from cardiac surgery. In some patients the pericardial effusion is

circumcardiac but in others the effusion is loculated posterior to the heart, because of anterior intrapericardial adhesions.¹⁻⁴ We describe a new 2-dimensional echocardiograph-

ic sign that appears specific for large posterior loculated effusions with tamponade: in the long-axis view (parasternal or apical) no pericardial space is seen anterior to the heart, but a large sonolucent space is seen

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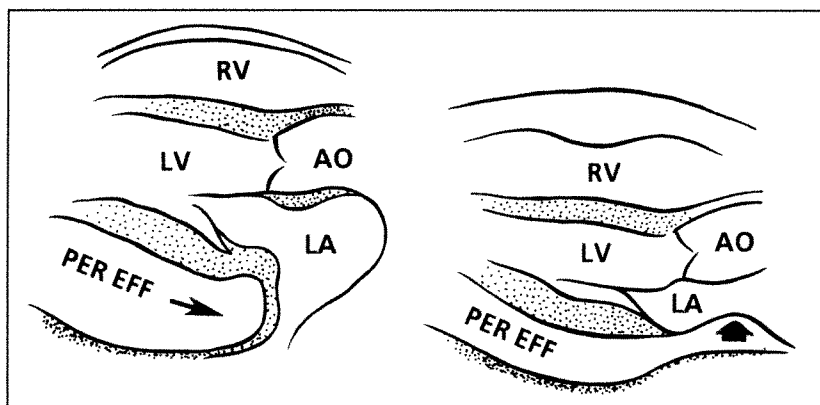


FIGURE 1. Parasternal long-axis view in tamponade due to large loculated posterior pericardial effusion (PER EFF) (left) and to large circumcardiac pericardial effusion (right). Distension of the oblique pericardial sinus (long arrow) distorting the left atrium (LA) is seen in the former but not the latter. Phasic left atrial posterior wall indentation (compression) by pericardial fluid (thick arrow) may be seen during late diastole-early systole in tamponade due to circumcardiac non-loculated pericardial effusion (right). AO = aorta; LV = left ventricle; RV = right ventricle.

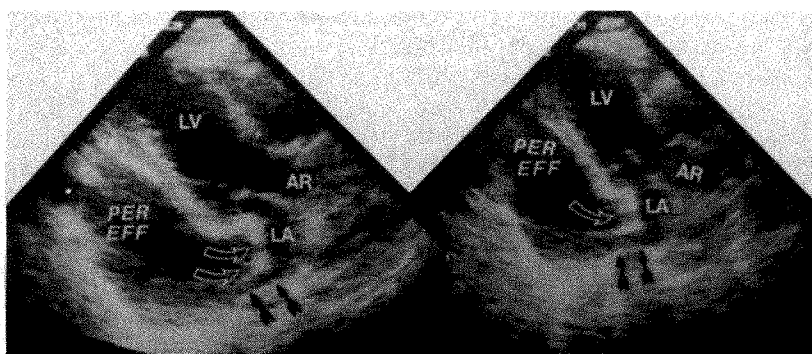


FIGURE 2. Long-axis views from the 2-dimensional echocardiogram of a large posterior loculated pericardial effusion (PER EFF) with tamponade. White arrows indicate the distended oblique pericardial sinus, distorting the left atrial shape. Black arrows show a stretched left pulmonary vein entering the left atrium (LA). Left atrial deformation is better seen on the left, whereas the prominent stretched pulmonary vein is better defined on the right. AR = aortic root; LV = left ventricle.

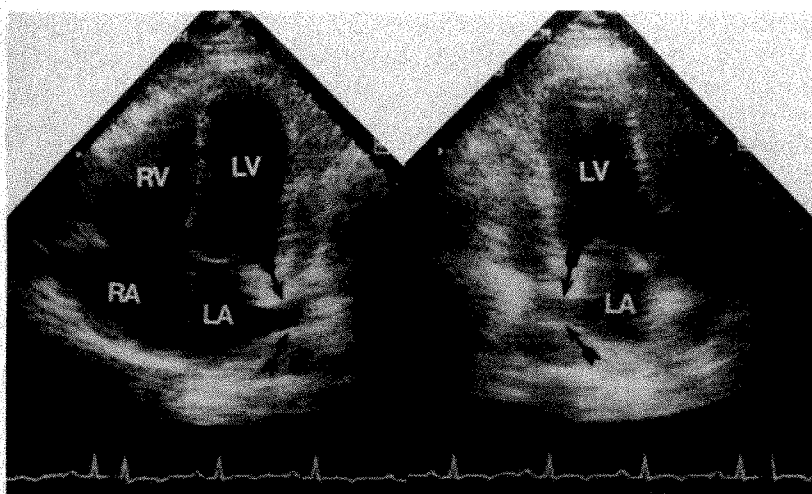


FIGURE 3. Two-dimensional echocardiogram of the same patient as in Figure 2. The apical 4-chamber view is shown on the left; the apical view on the right is in an unconventional plane. In both views the plane selected was such that it demonstrated a prominent (presumably stretched) left pulmonary vein (black arrows) entering the left atrium (LA). RA = right atrium; other abbreviations as in Figure 1.

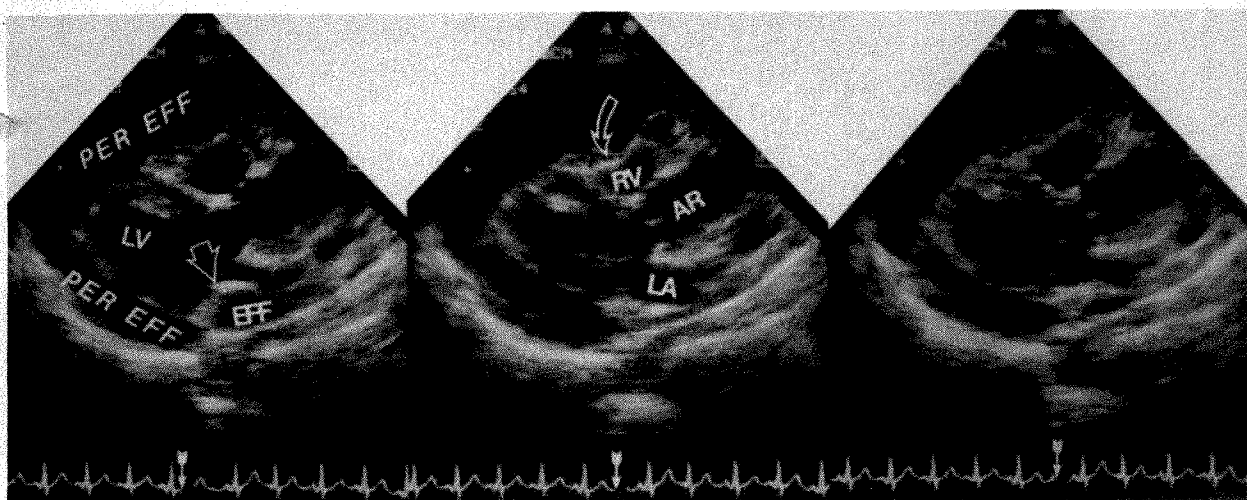


FIGURE 4. Two-dimensional echocardiogram in the parasternal long-axis view of a patient with tamponade due to a large circumcardiac pericardial effusion (PER EFF). The 3 frames are serial ones from the same cardiac cycle (small white arrows on electrocardiogram indicate timing). The left frame shows left atrial compression in very early systole (short open arrow). In the center frame, left atrial indentation is no longer seen, but right ventricular (RV) wall compression is evident. Some left atrial indentation is again seen later in diastole (right frame). AR = aortic root; LA = left atrium; LV = left ventricle.

posteriorly, representing a loculated pericardial effusion. The oblique sinus is grossly distended (Figure 1), resulting in left atrial distortion, so that its shape is altered from the normal biconvex to a concave-convex (reversed C) contour in this view (Figure 2). In 3 patients, we noted that left pulmonary veins were abnormally stretched by the contiguous distended oblique pericardial sinus and therefore unduly conspicuous (Figure 3). The pulmonary veins and their entry into the left atrium were identified by color-flow Doppler.

We noted distension of the oblique pericardial sinus on the 2-dimensional echocardiogram in 5 patients with large loculated posterior pericardial effusions after coronary bypass surgery. In 3 of these 5 patients, the diagnosis of tamponade was based on cardiac catheterization findings typical of tamponade (elevated and similar [within 4 mm Hg] diastolic pressures in the right heart and pulmonary artery wedge). Subxiphoid surgical drainage was performed in these 3 patients with relief of tamponade. In the 2 other patients, tamponade was diagnosed because of a decrease in the systemic systolic pressure of 25 to 30 mm from baseline level. In one of these patients, the pericardial effusion was drained surgically by the subxiphoid route. In the other patient, judged to have mild tamponade, management

was nonsurgical; serial echocardiograms over several weeks showed gradual spontaneous resolution.

Distension of the oblique pericardial sinus was not observed in 20 patients with moderate to large postoperative loculated posterior pericardial effusions (width of posterior pericardial space >2 cm) who did not have clinical evidence of tamponade. With conservative follow-up without drainage, they recovered uneventfully from coronary bypass surgery. No oblique sinus distension was found in 8 patients with tamponade due to circumcardiac pericardial effusions, all of whom had prompt regression of signs of tamponade after drainage of the pericardial effusion.

The oblique pericardial sinus is a potential pericardial space or recess posterior to the left atrium, into which pericardial fluid may extend in large effusions. Right atrial compression is a well-known manifestation of tamponade in large circumcardiac pericardial effusions; it is less widely known that left atrial compression, although less conspicuous and apparently less common, can likewise occur in this type of tamponade.^{5,6} In such circumstances, inward motion of right as well as left atrial walls is phasic; that is, it occurs in late diastole-early systole, but is absent during the rest of the cardiac cycle (Figure 4). The left atrial posterior wall

contour change and its timing is thus quite different from oblique sinus distension, which we describe here in patients with tamponade due to posterior loculated pericardial effusions. The latter causes gross distortion of the atrial contour in the long-axis view, which persists with little change through the entire cardiac cycle.

We conclude that distension of the oblique pericardial sinus is, in our experience, specific for tamponade in patients with postcardiac surgery pericardial effusions. Two-dimensional echocardiography demonstrates, in addition, stretching of pulmonary veins in such cases. Patients with postsurgical nonloculated pericardial effusions producing tamponade may show transient phasic left atrial collapse but do not show oblique sinus distension.

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Myocardial fibrosis and pathologic hypertrophy in the rat with renovascular hypertension; 1G

Principles of antihypertensive drug treatment; 82G

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Discussion III: effects in malignant ventricular arrhythmias; 65A

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Discussion I: pharmacology, pharmacodynamics and pharmacokinetics of sotalol; 35A

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Effects of sotalol on ventricular tachycardia and fibrillation produced by programmed electrical stimulation: comparison with other antiarrhythmic agents; 53A

Expanding clinical role of unique class III antiarrhythmic effects of sotalol; 84A

Hemodynamic effects of intravenous and oral sotalol; 28A

Historical development of the concept of controlling cardiac arrhythmias by lengthening repolarization: particular reference to sotalol; 3A

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Pharmacology, pharmacodynamics and pharmacokinetics of sotalol; 12A

Safety and efficacy of sotalol in patients with drug-refractory sustained ventricular tachyarrhythmias; 58A

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Symposium: Evolving Issues in the Treatment of Hypercholesterolemia

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At what levels of total low- or high-density lipoprotein cholesterol should diet/drug therapy be initiated? European Guidelines; 11F

Can atherosclerotic lesions regress? Angiographic evidence in humans; 41F

Can atherosclerotic plaques regress? Anatomic and biochemical evidence from nonhuman animal models; 33F

Clinical benefits and cost-effectiveness of lowering serum cholesterol levels: the case of simvastatin and cholestyramine in the Netherlands; 27F

Clinical experience with lovastatin; 23F

Diffuse extent of coronary atherosclerosis in fatal coronary artery disease; 2F

Hydroxymethylglutaryl coenzyme A reductase inhibitors as monotherapy in the treatment of hypercholesterolemia; 19F

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Lipid-lowering therapy after an atherosclerotic event; 16F

Symposium: Hormone-Electrolyte Interactions in Congestive Heart Failure

Cardiac glycosides and congestive heart failure; 10E

Discussion; 22E

Final discussion; 52E

Hormone-electrolyte interactions in congestive heart failure: lessons from a 4,000-year-old sumerian tablet; 1E

Hypokalemia and cardiovascular disease; 4E

Interaction of diuretics and electrolytes in congestive heart failure; 17E

Interaction of the sympathetic nervous system and electrolytes in congestive heart failure; 24E

Interrelation of electrolytes and renin-angiotensin system in congestive heart failure; 28E

Potassium and ventricular arrhythmias; 33E

Potential role of potassium as a determinant of morbidity and mortality in patients with systemic hypertension and congestive heart failure; 45E

Symposium: Indapamide and Antihypertensive Strategy

Antihypertensive strategy: a current and prospective review; 2H

Cardiovascular effects of antihypertensive drugs—involvement in the therapeutic choice; 33H

Cardiovascular protective properties of indapamide; 11H

Clinical efficacy and quality of life with indapamide, alone or in combination with beta blockers or angiotensin-converting enzyme inhibitors; 62H

Diuretics and the treatment of systemic hypertension; 72H

Diuretics and transmembrane ionic exchanges: structure-activity relations and clinical applications; 55H

Effects of indapamide on endothelium-dependent relaxations in isolated canine femoral arteries; 6H

Effects of indapamide on left ventricular mass and function in systemic hypertension with left ventricular hypertrophy; 37H

Effects of indapamide on lipoproteins and apoproteins in ambulatory hypertensive patients; 77H

Effects of indapamide on the mechanical properties of the arterial wall in deoxycorticosterone acetate-salt hypertensive rats; 28H

Efficacy of antihypertensive treatment with indapamide in patients with noninsulin-dependent diabetes and persistent microalbuminuria; 46H

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Long-term diuretic therapy and renal function in essential arterial hypertension; 51H

Long-term effects of indapamide: final results of a two-year Italian multicenter study in systemic hypertension; 67H

Role of metabolic risk factors in cardiovascular prognosis of systemic hypertension; 43H

Twenty-four-hour blood pressure monitoring and effects of indapamide; 58H

Symposium: Pharmacologic Management of Ventricular Arrhythmias—Current Status in the Role of Moricizine HCl

Antiarrhythmic drug therapy for congestive heart failure with focus on moricizine; 56D

Cardiac electrophysiologic effects of moricizine hydrochloride; 15D

Clinical development of moricizine as an antiarrhythmic agent; 11D

Clinical pharmacokinetics of moricizine; 21D

Comparisons of efficacy and tolerance of moricizine with other antiarrhythmic agents in the treatment of chronic ventricular arrhythmias; 32D

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Proarrhythmic potential of moricizine: strengths and limitations of a data base analysis; 51D

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Clinical implications of new studies in the treatment of benign, potentially malignant and malignant ventricular arrhythmias; 36B

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Sudden arrhythmic cardiac death—mechanisms, resuscitation and classification: the Seattle perspective; 4B

Sudden cardiac death: a diversity of causes with focus on atherosclerotic coronary artery disease; 13B

The AJC and television: a logical marriage; 3B

The cardiac arrhythmia suppression trial: background, interim results and implications; 20B

Symposium: The Renin-Angiotensin System—Tissue-Specific Issues

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Captopril and enalaprilat do not scavenge the superoxide anion; 24I

Issues surrounding a local cardiac renin system and the beneficial action of angiotensin-converting enzyme inhibitors in the ischemic myocardium; 11I

Myocardial ischemia reperfusion and free radical injury; 14I

Neuroendocrine activation after acute myocardial infarction; 28I

Neuroendocrine activation in acute myocardial infarction; 32I

Protection of the myocardium during myocardial infarction: pharmacologic protection during thrombolytic therapy; 35I

Renal protective effects of angiotensin-converting enzyme inhibition; 49I

The angiotensin-converting enzyme inhibitor: a drug for all seasons; 1I

Tissue renin-angiotensin systems in the heart and vasculature: possible involvement in the cardiovascular actions of converting enzyme inhibitors; 3I

Symposium: Thrombosis and Antithrombotic Therapy—Direction for the '90s

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Antithrombin therapy in historical perspective; 2C

Antithrombotic therapy in cardiac disease: an approach based on pathogenesis and risk stratification; 38C

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Rest and exercise cardiovascular effects of terazosin in congestive heart failure; 638

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Before prescribing, please see full prescribing information.
Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, $p=0.056$).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group ($p=0.06$; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones have not been

3. Since a reduction of mortality from coronary artery disease has been increased in demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p=0.1$). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2%

(23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: **Gastrointestinal:** cholestatic jaundice; **Central Nervous System:** dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; **Eye:** blurred vision; **Genitourinary:** impotence; **Musculoskeletal:** myopathy, myasthenia, myalgia, painful extremities, arthralgia, myositis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); **Clinical Laboratory:** increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; **Hematopoietic:** anemia, leukopenia, bone marrow hypoplasia, eosinophilia; **Immunologic:** angioedema, laryngeal edema, urticaria; **Integumentary:** exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: **General:** weight loss; **Cardiac:** extrasystoles; **Gastrointestinal:** pancreatitis, hepatoma, colitis; **Central Nervous System:** convulsions, syncope; **Eye:** retinal edema; **Genitourinary:** decreased male fertility; **Clinical Laboratory:** positive antinuclear antibody; **Hematopoietic:** thrombocytopenia; **Immunologic:** anaphylaxis, Lupus-like syndrome, vasculitis; **Integumentary:** alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdose, symptomatic supportive measures should be taken should it occur.

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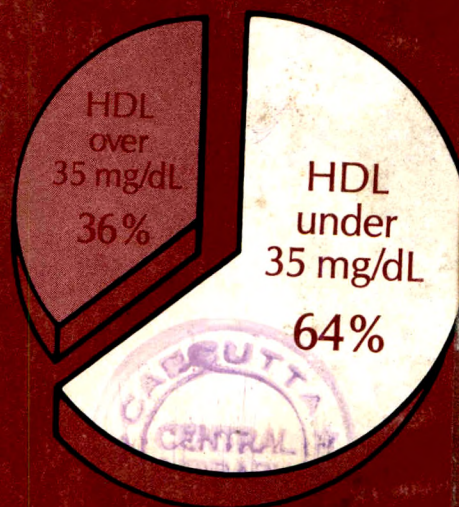
400 TOTAL

<35 HDL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,¹ and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.²

HEART ATTACK PATIENTS
(PROCAM TRIAL)²



LOPID raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).³

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).³

A powerful case for

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BID
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RAISES HDL...DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. 2. Assmann G, Schulte H. PROCAM-Trial: Prospective Cardiovascular Münster Trial. Zürich: Panscientia Verlag; 1986:8-9. 3. Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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